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International Clinical Practice Guidelines for Gender Minority/Trans People: Systematic Review and Quality Assessment

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Structured abstract

Objectives: To identify and critically appraise published clinical practice guidelines (CPGs) regarding health care of gender minority/trans people.

Design: Systematic review and quality appraisal using AGREE II (Appraisal of Guidelines for Research and Evaluation tool), including stakeholder domain prioritisation.

Setting: Six databases and six CPG websites were searched, and international key opinion leaders approached.

Participants: CPGs relating to adults and/or children who are gender minority/trans with no exclusions due to comorbidities, except differences in sex development.

Intervention: Any health-related intervention connected to the care of gender minority/trans people.

Main outcome measures: Number and quality of international CPGs addressing the health of gender minority/trans people, information on estimated changes in mortality or quality of life (QoL), consistency of recommended interventions across CPGs, and appraisal of key messages for patients.

Results: Twelve international CPGs address gender minority/trans people's healthcare as complete (n=5), partial (n=4) or marginal (n=3) focus of guidance. The quality scores have a wide range and heterogeneity whichever AGREE II domain is prioritised. Five higher-quality CPGs focus on HIV and other blood-borne infections (overall assessment scores 69-94%). Six lower-quality CPGs concern transition-specific interventions (overall assessment scores 11-56%). None deal with primary care, mental health, or longer-term medical issues. Sparse information on estimated changes in mortality and QoL is

conflicting. Consistency between CPGs could not be examined due to unclear recommendations within the World Professional Association of Transgender Health Standards of Care Version 7 and a lack of overlap between other CPGs. None provide key messages for patients.

Conclusions: A paucity of high-quality guidance for gender minority/trans people exists, largely limited to HIV and transition, but not wider aspects of healthcare, mortality or QoL. Reference to AGREE II, use of systematic reviews, independent external review, stakeholder participation and patient facing material might improve future CPG quality.

Trial registration: PROSPERO (CRD42019154361)

Article summary

Strengths and limitations of this study

- First systematic review to identify and use a validated quality appraisal instrument to assess all international CPGs addressing gender minority/trans health.
- International CPGs were studied due to their influential status in gender minority/trans health, though further research is needed on national and local CPGs.
- An innovative prioritisation exercise was performed to elicit stakeholders' priorities and inform the setting of AGREE II quality thresholds, however those stakeholder priorities may not be applicable outside the UK.
- An inclusive approach using wide criteria, extensive searches and approaching key opinion leaders should have allowed the study to identify all relevant international CPGs, however it is possible some may have been missed.

Introduction

Assessing the quality of clinical practice guidelines

Evidence-based practice integrates best available research with clinical expertise and the patient's unique values and circumstances. High-quality clinical practice guidelines (CPGs) support high quality health care delivery. They can guide clinicians and policy makers to improve care, reduce variation in clinical practice, thereby affecting patient safety and outcomes. The Institute of Medicine defines CPGs as: "statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options"[1], though other definitions exist[2]. Recommendations are used alongside professional judgement, directly or within decision aids, in training and practice. CPGs are important but have limitations depending on evidence selection and development processes[3]. GRADE (Grading of Recommendations, Assessment, Development and Evaluation) was developed to address the evidence that is selected and appraised during CPG development[4–6]. Using a systematic approach and transparent framework for developing and presenting summaries of evidence, GRADE is the most widely adopted tool worldwide for grading the quality of evidence and making recommendations[7], but does not alone ensure a CPG is high quality. Strength of evidence is only one component of what makes a 'good' CPG; factors such as transparency, rigour, independence, multidisciplinary input, patient and public involvement, avoidance of commercial influences and rapidity[8,9] should be also considered. Broader domains of CPG quality are included in the Appraisal of Guidelines for Research and Evaluation instrument AGREE II[10–12]. Despite widely recognized principles and methods for developing

sound CPGs, current research shows that guidelines on various topics lack appropriate uptake of systematic review methodologies in their development[13], give recommendations that conflict with scientific evidence[14], or do not adequately take into account existing CPG quality and reporting assessment tools[15]. This emphasizes the ongoing need to appraise guidelines to ensure evidence-informed care.

Healthcare for gender minority/trans people

'Trans' is an umbrella term for individuals whose inner sense of self (gender identity) or how they present themselves using visual or behavioural cues (gender expression) differs from the expected stereotypes (gender) culturally assigned to their biological sex[16]. Gender minority is an often-used alternative population description. Some gender minority/trans people may seek medical transition, which involves interventions such as hormones or surgery that alter physical characteristics and align appearance with gender identity. Patient numbers referred to UK gender identity clinics and length of waiting lists have increased in the last decade, particularly for adolescents[17], a phenomenon seen elsewhere[18]. Gender minority/trans people may have continuing, sometimes complex, life-long healthcare needs whether they undergo medical transition or not. Gender minority/trans people may experience more mental health issues such as mood and anxiety disorders[19], substance use[20], and higher rates of suicidal ideation[21]. They may seek assistance with sexual health, mental health[22], substance use disorders[23], prevention and/or management of HIV[24] as well as usual general health enquiries. However, they may encounter difficulties in accessing healthcare[25], reporting negative healthcare experiences[26], discrimination and stigma[30,31]. Like all individuals,

gender minority/trans people require high-quality evidence-based healthcare[25,29] addressing general and specific needs.

Guidelines used internationally and in the UK

The quality of current guidelines on gender minority/trans health is unclear. The World Professional Association for Transgender Health (WPATH) Standards of Care Version 7 (SOCv7)[30] represent normative standards for clinical care, acting as a benchmark in this field[31]. Globally, many national and local guidelines[32–35] are adaptations of, acknowledge being influenced by, or are intended to complement WPATH SOCv7[30], despite expressed reservations that WPATH SOCv7[30] is based on lower-quality primary research, the opinions of experts and lacks grading of evidence[36].

In the UK, an advocacy group worked to incorporate WPATH SOCv7[30] into national practice[37]. WPATH SOCv7[30] informs National Health Service (NHS) gender identity clinics[38] and guidelines produced by the Royal College of Psychiatrists (without use of GRADE)[39]. No CPGs were available from the National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), British Association of Gender Identity Specialists, British Psychological Society or other medical Royal Colleges, although the Royal College of General Practitioners issued a position statement on gender minority/trans healthcare in 2019[40]. Assessing quality of international CPGs such as WPATH SOCv7[30] has practice implications for the NHS[38] and private sector. CPGs with international scope may present additional challenges (e.g. the implementability of key recommendations might not be easily translated among different contexts) but they seem to influence discourse around gender minority/trans health[36]. No prior study has investigated the number and quality of

guidelines to support the care and well-being of gender minority/trans people. The purpose of this research was to identify and critically appraise all published international CPGs for the healthcare of gender minority/trans people.

Methods

Approach/ Research Design

The rationale was to identify the key CPGs available to healthcare practitioners in this field of clinical practice. Following preliminary searches, we chose international CPGs in view of WPATH's influence within the UK and elsewhere, and to avoid 'double-counting'. We considered AGREE II[10–12] the most appropriate tool; it is the most comprehensively validated and evaluated instrument available for assessing CPGs[41,42], designed for use by non-expert stakeholders[10] such as healthcare providers, practicing clinicians and educators[11]. It benefits from clear instructions and prompts regarding scoring and several people applying the criteria independently. AGREE II synthesis calculates quality scores from 23 appraisal criteria organised into six key domains (scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, editorial independence) and an overall assessment of "Recommend for use?" (Answer options; yes, no, yes if modified). This systematic review was conducted according to a pre-specified PROSPERO protocol (CRD42019154361)

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=154361uploaded 19th December 2019. The MEDLINE strategy was straightforward; although not formally processed[43], it was peer-reviewed by one information specialist.

Inclusion and exclusion criteria

We defined CPGs as a systematically developed set of recommendations that assist practitioners and patients in the provision of healthcare in specific circumstances, produced after review and assessment of available clinical evidence[1,2,44–46]. CPGs published after 1st January 2010 were eligible if they (or part thereof) specifically targeted patients/population with gender minority/trans status and/or gender dysphoria, were evidence-based, with some documentation of development methodology, had international scope (more than one country, defined as a Member State of the United Nations), and were an original source. We chose the timeframe to focus on the most recent guidelines, currently applicable to practice, and to include WPATH SOCv7[30]. CPGs were eligible if they met the following inclusion criteria: participants/population was adults and/or children who are gender minority/trans with no exclusion due to comorbidities or age although differences/disorders in sex development (intersex) were excluded; exposure/intervention was any health intervention related to gender dysphoria or gender affirmation, or health concerns of gender minority/trans people, including screening, assessment, referral, diagnosis and interventions. We used broad criteria because terminology has been in flux with changes made in both ICD and DSM diagnostic criteria[16]. There were no restrictions on setting or language.

Search strategy and guideline selection

We conducted the searches up to 11th June 2020 (CM), using search terms and appropriate synonyms (as MeSH terms and text words) that we developed based on population and exposures (Web/Supplementary Table 1). We searched six databases

(EMBASE, MEDLINE, Web of Science, PsycINFO, CINAHL, LILACS) and six CPG websites (Agency for Healthcare Research and Quality National Guideline Clearinghouse [NGC], eGuidelines and Guidelines, National Institute for Health and Care Excellence National Library for Health, Scottish Intercollegiate Guidelines Network, EBSCO DynaMed Plus, Guidelines International Network Library) and the World Health Organisation (WHO). The NGC closed in 2017 but CM hand-searched the archive. In addition to protocol, individual reviewers (IA, DC, MJ) hand-searched four specialty journals (International Journal of Transgender Health, Transgender Health, LGBT Health, Journal of Homosexuality). In order to find potential grey literature CPGs outwith the scholarly literature, two reviewers (IA, SD) independently performed four separate Google searches (not GoogleScholar as mistated in the protocol) by using one generic (clinical practice guidelines) plus one specific term (transgender, gender dysphoria, trans health, or gender minority) and examining the first 100 hits. We identified International Key Opinion Leaders via publications known to reviewers (DC, SD) (n=24) and contacted them via one email and reminder to identify further guidelines. Reference lists of relevant reviews and all full-text studies were hand-searched to identify any relevant papers or CPGs not found by database searching. Two reviewers (SB, SD) independently read all titles and abstracts and assessed for inclusion. If there was uncertainty or disagreement, or reasonable suspicion that the full-text might lead to another relevant CPG, the full-text was obtained. Non-English abstracts were Google-translated but if a possible CPG could not be reliably excluded, the full-text paper was obtained and translated. Where full-text publications could not be accessed, we contacted authors directly. Two reviewers (SB and either DC/MJ) independently carried out full-text

assessment to determine inclusion or exclusion from the systematic review based on the above criteria, and noted reasons for excluding full-texts. The whole team discussed uncertainties and disagreements to achieve consensus, with voting and final adjudication by the senior author (CM).

Data extraction

Two reviewers (SB, SD) independently collected formal descriptive data of included CPGs. All ambiguities or discrepancies were referred to the team for discussion and to re-examine original texts and extract data. Information collected was title, author, year of publication, number of countries covered, originating organisation, audience, methods used, page and reference numbers (excluding accompanying materials), and funding. Key recommendations were extracted for comparison between CPGs. We searched for all text mentions of mortality or any measures of quality of life (QoL), and noted if accompanied by a citation. All patient facing material was extracted. In addition, we extracted data about publication outlet (journal/website), and whether the quantity of information pertaining to the health of gender minority/trans people represented a complete, partial or marginal proportion of recommendations in the CPG.

Outcomes

Outcomes were: the number and quality assessment (using AGREE II) of international CPGs addressing the health of gender minority/trans people; analysis and comparison of the presence or absence of information on estimated changes in mortality or QoL (any measure) following any specific recommended intervention, over any time interval; the consistency (or lack thereof) of recommendations across the CPGs; and the presence (or absence) of key messages for patients.

Quality assessment

All authors completed AGREE II video training, a practice assessment, and two pilots whose results were discussed. The six reviewers independently and anonymously completed quality scoring by using the standard proforma (myAgree Plus platform, AGREE Enterprise website)[11].

Patient and Public Involvement

The AGREE II instrument generates quality scores but does not set specific parameters for what constitutes high quality, recommending that decisions about defining such thresholds should be made prior to performing appraisals, considering relevant stakeholders and the context in which the CPG is used[11]. To help set quality thresholds, we conducted an AGREE II domain prioritisation exercise in January 2020 via email, with one reminder. It was considered impossible to ensure comprehensive representation of international stakeholders. We chose the UK for feasibility, albeit validity might be limited to the NHS. Fifty-two UK service-user stakeholder groups and gender minority/trans advocacy organisations, identified via reviewer knowledge and internet searches (IA, SB, DC, SD, MJ, CM), were informed about the study. They were invited to participate in a stakeholder prioritisation of the AGREE II domains, created using SurveyMonkey® and with an option to remain anonymous (https://www.surveymonkey.co.uk/r/WLZ55NQ gives invitation wording, links to resources and protocol). The reviewer team performed an anonymous prioritisation for comparison.

Strategy for Data and Statistical Analyses

Simple frequencies were used to present the stakeholder and reviewer priorities, and outcomes. Following team discussion of the prioritisation exercise results, no pre-specified quality threshold score was used to define high or low quality, although colour was superimposed (≤30%, 31-69% and ≥70%) on the final scores table to aid visual comparisons and interpretation.

Results

Search results

Figure 1 (PRISMA flow chart[47]) shows that 1,815 citations were identified, of which 134 full-text publications were read (all available, three supplied by authors) and 122 excluded (Supplementary Table W2 with reasons).

Data extraction

Table 1 shows the characteristics of the CPGs. Supplementary Tables W3 and W4 show raw data of key recommendations and mortality and QoL evidence.

Number and characteristics of Clinical Practice Guidelines

Twelve CPGs (Table 1) originated from: WHO (n=3)[48–50], WPATH (n=2)[30,51], professional specialist/special-interest societies (n=4)[52–55], small groups of experts (n=2)[56,57] and one consortium[58]. All were published in English, in journals[51–57], the organisation's website[48–50,58], or both[30]. Guideline development methodology was variable, including use of systematic reviews (Table 1). Ten CPGs had no external review, eight had no update plans. Gender minority/trans health recommendations made up complete (n=5)[30,51,53,55,57], partial (n=4)[48–50,56] or marginal (n=3)[52,54,58] focus of content. CPGs contained 10 to 155 pages, and 20 to 505 references. Funding

sources were wide-ranging and sometimes multiple, from government agencies, professional societies, charities and private donations. Two CPGs provided no funding details[52,56].

Table 1. General characteristics of included Clinical Practice Guidelines (n = 12)

Number	Author (year)	Full title	Countries covered	Origin	Primary Audience	Design (systematic review, SR, used and methods thereafter)	Planned update given	Funding
1	Coleman et al. (2012)	Standards of care for the health of transsexual, transgender, and gender nonconforming people v7	Global	WPATH	Health professionals	Work groups submit manuscripts based on prior literature reviews, no explicit links of recommendations to evidence, expert consensus. No independent external review	No	Tawani Foundation and gift from anonymous donor
2	Davies et al. (2015)	Voice and communication change for gender nonconforming individuals: giving voice to the person inside	Global	WPATH	Speech-language therapists	Review of evidence. Expert consensus. No independent external review	No	Transgender Health Information Program of British Columbia Canada
3	ECDC (2018)	Public health guidance on HIV, hepatitis B and C testing in the EU/EEA	EU/ EEA	ECDC consortium CHIP, PHE, SSAT and EATG	Member States' Public Health Professionals who coordinate the development of national guidelines or programmes for HBV, HCV and HIV testing	4 SRs, SIGN, NICE and AXIS checklists. Ad hoc internal and external expert panel, independent chair, expert consensus. No independent external review	No	Commissioned by ECDC, contractor Rigshopitalet CHIP
4	Gilligan et al. (2017)	Patient-clinician communication: American Society of Clinical Oncology consensus guideline	USA and others	ASCO	Clinicians who care for adults with cancer	9 questions (1 SR), expert consensus and a Delphi exercise. No independent external review	Regular review 3 yr check	None declared
5	Hembree et al. (2017)	Endocrine treatment of gender-dysphoric/ gender-incongruent persons: An Endocrine Society clinical practice guideline	Global	Endocrine Society	Endocrinologists, trained mental health professionals and trained physicians	2 SRs and GRADE, rest expert consensus. No independent external review	No	Endocrine Society
6	IAPHCCO (2015)	IAPAC Guidelines for optimizing the HIV care continuum for adults and adolescents	Global	IAPAC	Care providers, program managers, policymakers, affected communities, organizations, and health systems involved with	A systematic search of CDC database, expert consensus. No independent external review	No	IAPAC, US NIH and Office of AIDS Research

					implementing HIV programs and/or delivering HIV care			
7	Ralph et al. (2010)	Trauma, gender reassignment and penile augmentation	Not specified (international publication)	Author group	Not stated (urological surgeons)	No SR. Unclear if literature review. Leading experts' consensus opinion. No independent external review	No	None declared
8	Strang et al. (2016)	Initial clinical guidelines for co-occurring autism spectrum disorder and gender dysphoria or incongruence in adolescents	Not specified (international publication)	Author group	Clinicians	No SR or literature review. 2-stage Delphi consensus. No independent external review	No	Isadore and Bertha Gudelsky Family Foundation
9	T'SJoen	ESSM Position Statement "Assessment and hormonal management in adolescent and adult trans people, with attention for sexual function and satisfaction"	Europe	ESSM	European clinicians working in transgender health, sexologists and other health-care professionals	No SR. Leading experts' consensus opinion. No independent external review	No	ESSM
10	WHO (2011)	Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people. Recommendations for a public health approach	Global	WHO	National public health officials and managers of HIV/AIDS and STI programmes, NGOs inc. community and civil society organizations, and health workers	13 SRs for PICOs and GRADE, external GDG, and independent external review	Yes in 2015	BMZ & PEPFAR through CDC & USAID
11	WHO (2012)	Guidance on oral pre-exposure prophylaxis for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV. Recommendations for use in the context of demonstration projects	Global	WHO	Countries/ Member States	4 SRs (inc values and preferences reviews) and GRADE, external GDG, and independent external review group	Yes in 2015	Bill and Melinda Gates Foundation
12	WHO (2016)	Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. 2016 update	Global	WHO	National HIV programme managers and other decision-makers within ministries of health and those responsible for health policies, programmes and services in prisons.	2 new SRs in revised guidance, GRADE, external GDGs, and 79 independent external peer reviewers	Regular updates; no detail	UNAIDS, PEPFAR, Global Fund

Key: AACE, American Association of Clinical Endocrinologists; ASA, American Society of Andrology; ASCO, American Society of Clinical Oncology; ASD, autism spectrum disorder; AXIS, Appraisal Tool for Cross-Sectional Studies; BMZ, German Federal Ministry for Economic Cooperation and Development; CDC, the Centers for Disease Control and Prevention; CHIP, CHIP/Region H, Rigshospitalet, University of Copenhagen; CPG, clinical practice guideline; EATG, European Aids Treatment Group; EAU, European

Association of Urology; ECDC, European Centre for Disease Prevention and Control; ESE, European Society of Endocrinology; ESPE, European Society for Pediatric Endocrinology; ESSM, European Society for Sexual Medicine EU/EEA, European Union/ European Economic Area; Global Fund, Global Fund to Fight AIDS, Tuberculosis and Malaria; GDG, guideline development group; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IAPAC, International Association of Providers of AIDS Care; IAPHCCO, International advisory panel on HIV care continuum optimization; NGO non governmental organisations; NICE, National Institute of Health and Care Excellence; NIH, National Institutes of Health; PEPFAR, US President's Emergency Plan for AIDS Relief; PES Pediatric Endocrine Society; PHE, Public Health England; SIGN, Scottish Intercollegiate Guidelines Network; SR, systematic review; SSAT, St Stephen's AIDS Trust; UNAIDS, The Unified Budget, Results and Accountability Framework of the Joint United Nations Programme on HIV/AIDS; USA, United States of America; USAID, US Agency for International Development; WHO, World Health Association; WPATH, World Professional Association for Transgender Health.

A thirteenth CPG was excluded post-scoring as it had been superseded by a 2020 version without recommendations for gender minority/trans people[59]. It was arguable if four included CPGs did meet criteria: one had not been withdrawn[48]; one contained minimal relevant content[52]; one might not have been intended as a CPG[30] (although WPATH SOCv7's stated overall goal is "to provide clinical guidance for health professionals"[30] it contains no list of key recommendations nor auditable quality standards, yet is widely used to compare procedures covered by US providers[60,61]); one variously described itself as 'position statement' and 'position study' (stating it did "not aim to provide detailed clinical guidelines for professionals such as… [named][30,53]", but evidence was obviously linked to key recommendations for clinicians[55]). After discussion it was decided not to exclude these borderline CPGs, as the definition of CPG in the protocol was intended to favour an inclusive approach.

Quality prioritisation and assessment

Results of the domain prioritisation by stakeholders (n=19 replies, response rate 39% excluding 3 'undeliverable') and reviewers (n=6) showed that stakeholders prioritised stakeholder involvement, whereas the research team prioritised methodological rigour (Supplementary Table W5). No stakeholder asked for clarification or more information.

Table 2 shows AGREE II scores by domain (8-94%), and overall (11-94%). The quality scores have a wide range and heterogeneity. Five CPGs focused on trans people as a key population for HIV and other blood-borne infections (overall assessment scores 69-94%). Six CPGs concerned transition-specific interventions (overall assessment scores 11-56%). Transition-related CPGs tended to lack methodological rigour and rely on patchier, lower-quality primary research. The two prioritised domain scores were usually

comparable with the overall AGREE II quality assessment (ranges; stakeholder involvement 14-93%, methodological rigour 17-87%). Four CPGs obtained a majority opinion 'recommend for use'[48–50,58], five CPGs had unanimous 'do not recommend'[30,51,55–57], and three had minority support with division about the extent of 'yes, if modified' [52–54](Table 2). Despite wide variation there was a pattern; HIV and blood-borne infection guidelines[48–50,54,58] were higher quality, and those focusing on transition were lower quality[30,53,55–57].

Table 2. AGREE II domain percentages and overall assessment of included guidelines, and summary of mortality/quality of life measures (n = 12)

Number	Author (year)	Scope and purpose	Stakeholder Involvement	Rigour of development	Clarity and presentation	Applicability	Editorial independence	Overall Assessment	Recommendation to use	Mortality	Quality of Life	Mortality (any comment) and Quality of Life (any formal measure)
1	Coleman et al. (2012)	63%	47%	20%	37%	16%	15%	31%	Yes **0** No **5** If modified **1**	Y	Y	M: Higher in post SRS vs matched no SRS, and both pre and post SRS vs. gen popn. QoL: FtM < gen popn, FtM post breast/chest surgery > not surgery, mixed results at 15 yrs.
2	Davies et al. (2015)	62%	38%	17%	61%	28%	14%	28%	Yes **0** No **3** If modified **3**	N	Y	QoL: A voice-related TG QoL measure correlated with own and others' perception.
3	ECDC (2018)	94%	56%	55%	76%	68%	38%	69%	Yes **4** No **0** If modified **2**	Y	Y	M: Reduced by early diagnosis. QoL: Cost/QALY in anti-HCV birth cohort screening is acceptable. Universal offer HIV testing in hospital settings is highly cost effective.
4	Gilligan et al. (2017)	84%	67%	66%	81%	47%	61%	78%	Yes **2** No **0** If modified **4**	N	N	
5	Hembree et al. (2017)	65%	40%	41%	73%	29%	65%	56%	Yes **1** No **2** If modified **3**	Y	Y	M: TW/TM's CV mortality same ("insufficient very low quality data" for TM) and younger age at death after SRS. QoL: long term psychological and psychiatric issues post SRS.
6	IAPHCCO (2015)	85%	56%	61%	87%	40%	63%	81%	Yes **3** No **0** If modified **3**	Y	Y	M: Lower if early ART, easy access, immediate ART, and community distribution. QoL: ART preserves QoL, and stigma and mental health impact on QoL.
7	Ralph et al. (2010)	45%	14%	19%	64%	5%	32%	28%	Yes **0** No **5** If modified **1**	N	N	
8	Strang et al. (2016)	57%	33%	19%	39%	8%	25%	11%	Yes **0** No **6** If modified **0**	N	N	
9	T'Sjoen et al. (2020)	59%	37%	35%	58%	15%	33%	42%	Yes **0** No 4 If modified 2	N	Y	QoL: Sexual life improves after GAMI, but not to non-TG levels.
10	WHO (2011)	94%	89%	87%	86%	64%	82%	83%	Yes **5** No **0** If modified **1**	Y	Y	M: Looked for mortality evidence but none found. QoL: Positive QALYs if HIV averted.
11	WHO (2012)	85%	60%	81%	76%	41%	72%	72%	Yes **4** No **0** If modified **2**	N	Y	QoL: Positive QALYs modelled if PrEP.
12	WHO (2016)	94%	93%	81%	89%	84%	65%	94%	Yes **5** No **0** If modified **1**	Y	N	M: Lower if access and adhere to OST and at prison release, if early ART and complete TB Rx, HBV/ HCV managed; and access to post abortion care. Worse if food insecure, poor nutrition, low BMI.

Key: ART, antiretroviral therapy; CV, cardiovascular; ECDC, European Centre for Disease Prevention and Control; FtM, female-to-male; gen popn, general population; GAMI, gender affirming medical intervention; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immuno-deficiency virus; IAPHCCO, International advisory panel on HIV care continuum optimization; M, mortality; OST, opiate substitute therapy; PrEP, pre-exposure prophylaxis; QALY, quality adjusted life year; QoL, Quality of life; Rx, treatment; SR, systematic review; SRS, sex reassignment surgery; TB, tuberculosis; TG, trans people/gender-minority; TM, trans man; TW, trans woman; WHO, World Health Association. Two prioritised domains for **stakeholders** **and** **research team**. Colours to aid interpretation (not thresholds) ≤30 RED, 31-69 AMBER, ≥70 GREEN

Content

Four CPGs concerning HIV prevention, transmission and care[48–50,54], and one public health guideline on population screening for blood-borne viruses[58], contained recommendations for gender minority/trans people as a 'key population'. Three CPGs were devoted to overall transition care for all gender minority/trans people[30,53,55], two to an aspect of transition[51,56], and one to transition in a specific group[57]. One oncology communication guideline contained a single recommendation relating to gender minority/trans people[52]. No international guidelines were found that addressed primary care, psychological support/mental health interventions, or general medical/chronic disease care (such as cardiovascular, cancer or elderly care).

Mortality and Quality of Life

Six CPGs referred to mortality[30,48,50,53,54,58] and eight to QoL[30,48,49,51,53–55,58] (Table 2). Supplementary Table W4 shows all extractions of sentences relating to mortality or morbidity, associated references and which CPGs included no such data. More robust evidence was linked to the recommendations in the HIV and blood-borne virus CPGs whereas there was little, inconsistent data and poorer linking to evidence in transition-related CPGs.

Consistency of recommendations across the CPGs

Supplementary Table W5 contains all extracted key recommendations where these could be distinguished. It shows little overlap of topic content across the CPGs. Many recommendations in WHO 2011[48] and 2016[50] were similar, but not identical, the former not being stood down after the latter was published. No statements were highlighted by the WPATH SOCv7[30] authors as key recommendations, and it proved

impossible for all six reviewers independently performing data extraction to identify them. The total number of extracted recommendations ranged between 0 to 168 with little consistency or agreement on what passages were selected. Some extracted statements might have been intended as recommendations or standards, but many were flexible, disconnected from evidence and could not be used by individuals or services to benchmark practice. After discussion of this incoherence within WPATH SOCv7[30] and our inability therefore to compare recommendations across all CPGs, it was decided not to revisit inclusions post hoc but to abandon this protocol aim.

Patient facing material

No patient-facing material was found in any guideline.

Discussion

Statement of principal findings

Variable quality international CPGs regarding gender minority/trans people's healthcare contain little, conflicting information on mortality and QoL, no patient facing messages and inconsistent use of systematic reviews in generating recommendations. A major finding is that the scope of the guidelines is confined to HIV/STI prevention or management of transition with an absence of guidelines relating to other medical issues. WPATH SOCv7[30] cannot be considered 'gold standard'.

Strengths and weaknesses of this study

Strengths include protocol preregistration, stakeholder involvement, piloting all stages, an extensive systematic search without language restriction for any relevant current guidelines, wide inclusion criteria including grey literature, use of key opinion leaders,

close attention to avoidance of bias, double full-text reading and data entry, and careful presentation of results. Six trained reviewers, exceeding AGREE II recommendations[11], compensated for expected variation in scoring. Extensive searches should have mitigated loss of CPGs. Limitations include some uncertainty about stakeholder understanding despite a good response rate, and generalisability of the prioritisation only to the UK; stakeholders elsewhere might have different priorities. Focusing only on international CPGs might have missed higher quality national and local CPGs derived from them or written de novo. The social acceptance and consequent healthcare system coverage of gender minority/trans health related interventions vary among different countries, which may limit the space for international and multinational guidelines. While the search strategy yielded an oncology communication CPG with a single recommendation for gender minority/trans people[52], other general health CPGs with similar solo statements might have been missed.

Comparison with other studies, discussing important differences in results

This is the first systematic review using a validated quality appraisal instrument of international CPGs addressing gender minority/trans health. It may act as a benchmark to monitor and improve population healthcare. CPG quality results correspond with, and quantitatively confirm, previously noted concerns about the evidence-base[36,62,63] and variable use of quality assessment in systematic reviews[64–66], in a healthcare field with unknown or unclear longitudinal outcomes[17]. AGREE II has been applied to CPGs in other medical areas, including cancer[67], diabetes[68], pregnancy[69] and depression[70]. These exercises tend to show room for improvement. Developers have been criticised for not using methodological rigour when writing reliable evidence-based

guidelines[71], as well as not implementing high-quality CPGs[72]. Thus, finding poor quality CPGs is not confined to this area of healthcare[73]. Improvement messages are generalisable to other specialties.

Meaning of the study: possible explanations

The finding of higher-quality, but narrow, focus on gender minority/trans people's healthcare for blood-borne infections may relate to the global HIV pandemic and the WHO applying twin lenses of public health and human rights (i.e. the population as 'means' and 'ends'). The lower-quality CPGs focus on transition. WPATH SOCv7[30] originated nearly a decade ago from a special-interest association, diagnostic criteria and CPG methodology have since changed. Although HIV and transition are important, it is puzzling to have found so little else, maybe suggesting CPGs for gender minority/trans people have been driven by provider-interests rather than healthcare needs. Including gender minority/trans people in guidelines can be considered a matter of health equity, where CPGs have a role to play[74]. GRADE suggests CPG developers may consider equity at various stages in creating guidelines, such as deciding guideline questions, evidence searching, and assembly of the guideline group[75]. How CPGs may impact more vulnerable members of society should be reflected-upon during guideline development[76], and implementation[77].

Implications for clinicians, UK and international policymakers, and patients

Clinicians should be made aware that gender minority/trans health CPGs outside of HIV-related topics are linked to a weak evidence base, with variations in methodological rigour and lack of stakeholder involvement. While patient care plans ought to take into account the individual needs of each gender minority/trans person, a gap appears to exist

between clinical practice and research in this field[78]. Clinicians should proceed with caution, explain uncertainties to patients and recruit to research.

Policymakers ought to invest in both primary research and high-quality systematic reviews in areas relevant for CPG and service development. Organisations producing guidelines and aspiring to higher-level quality could use more robust methods, handling of competing interests[79,80], and quality assessment. CPG developers should label key recommendations clearly. Although editorial independence was lowest priority for stakeholders, independent external review is important to avoid biases and bad practices, examine use of resources, resist commercial interests, and gain widespread credibility outside the field.

The UK is fortunate in being familiar with developing priority-setting partnerships (e.g. James Lind Initiative[81]) and generating suites of clinical questions that might cover all steps in patient pathways (e.g. in partnership with Cochrane Collaboration[82]). These could underpin multidisciplinary and funded research priorities whose results feed into future better evidence-based CPGs. Implications for UK education and curricular content (e.g. new gender identity healthcare credentials[83]), should be carefully scrutinised.

Internationally, CPG development and implementation will vary depending on local country contexts and available resources. Those countries with quality assurance agencies might use them for external assurance. Countries might reconsider the wisdom of adapting low-quality 'off the shelf' international CPGs without due assessment of the evidence for recommendations (e.g. using the GRADE Adolopment framework[84]). WHO demonstrates how CPGs can achieve high quality.

Patients should be positively encouraged to engage with CPG development as stakeholders. The lack of patient-facing material should be addressed, especially as medical and non-medical online material contains jargon, is unreliable and potentially misleading[85]. Future CPGs should be populated with patient-facing decision aids (e.g. Fact Boxes[86] and icon arrays[87]) that explain sizes of benefits and harms to support informed patient choice. Patients and carers will benefit from a more focused approach to throughout-life healthcare. As the figures for gender minority/trans patients increase within the NHS and internationally, so does the need for consistent guidance to clinicians across specialisms on specific risks to, and means of treating, this population. Current patients should be welcomed to contribute, where they are comfortable, to any research being undertaken by their clinicians, in order to improve data and future practice for gender minority/trans health.

Unanswered questions and future research

This study should be replicated as new iterations of international CPGs become available. It can be applied to national guidelines and countries should perform their own stakeholder prioritisation. When 'best available evidence' is poor, quality improvement can be driven both from inside and outside the field. International guideline developers require more primary research for this population, and impetus from clinicians and scientists to build a better evidence base using robust data from randomised controlled trials and long-term observational cohort studies, especially regarding chronic diseases, health behaviours, substance use, screening and how interventions (e.g. hormones) might impact on long-term health (e.g. risk of cardiovascular and thromboembolic disease).

Mortality and QoL data are required to address questions of clinical and cost-effectiveness.

Conclusion

Gender minority/trans health in current international CPGs seems limited to a focus on HIV or transition-related interventions. WPATH SOCv7[30] is due for updating and this study should be used positively to accelerate improvement. Future guideline developers might better address the holistic healthcare needs of gender minority/trans people by enhancing the evidence-base, upgrading the quality of CPGs and increasing the breadth of health topics wherein this population is considered.

Compliance with Ethical Standards

Contributorship statement: The authors were involved as follows: SB, IA, CM conception. All authors (SD, DC, IA, MJ, SB, CM) were involved in design, execution, analysis, drafting manuscript and critical discussion; all were responsible for revision and final approval of the manuscript. All authors had full access to all the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. CM acts as guarantor.

Competing interests statement: The authors had no financial support for this work. There were no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years and there were no other relationships or activities that could appear to have influenced the submitted work. All authors declare they have no conflict of interests. SB, SD & DC's declarations can be found at http://www.whopaysthisdoctor.org

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Transparency declaration: CM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned and registered have been explained.

Licence Statement

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80 Ioannidis JPA. Guidelines Do Not Entangle Practitioners With Unavoidable Conflicts as Authors, and When There Is No Evidence, Just Say So. *Circ Cardiovasc Qual Outcomes* 2018;**11**. doi:10.1161/CIRCOUTCOMES.118.005205

81 James Lind Alliance. About Priority Setting Partnerships. http://www.jla.nihr.ac.uk/about-the-james-lind-alliance/about-psps.htm (accessed 8 Jul 2020).

82 Thomas J, Kneale D, McKenzie J, *et al.* Chapter 2: Determining the scope of the review and the questions it will address. In: Higgins J, Thomas J, Chandler J, *et al.*, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane 2020. www.training.cochrane.org/handbook (accessed 11 Nov 2020).

83 Royal College of Physicians. Gender Identity Healthcare Credentials (GIH). RCP London. https://www.rcplondon.ac.uk/education-practice/courses/gender-identity-healthcare-credentials-gih (accessed 8 Jul 2020).

84 Schünemann HJ, Wiercioch W, Brozek J, *et al.* GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *J Clin Epidemiol* 2017;**81**:101–10. doi:10.1016/j.jclinepi.2016.09.009

85 Dunford C, Gresty H, Takhar M, *et al.* Transgender and adolescence: Is online information accurate or mis-leading? *Eur Urol Suppl* 2019;**18**:e1782. doi:10.1016/S1569-9056(19)31291-6

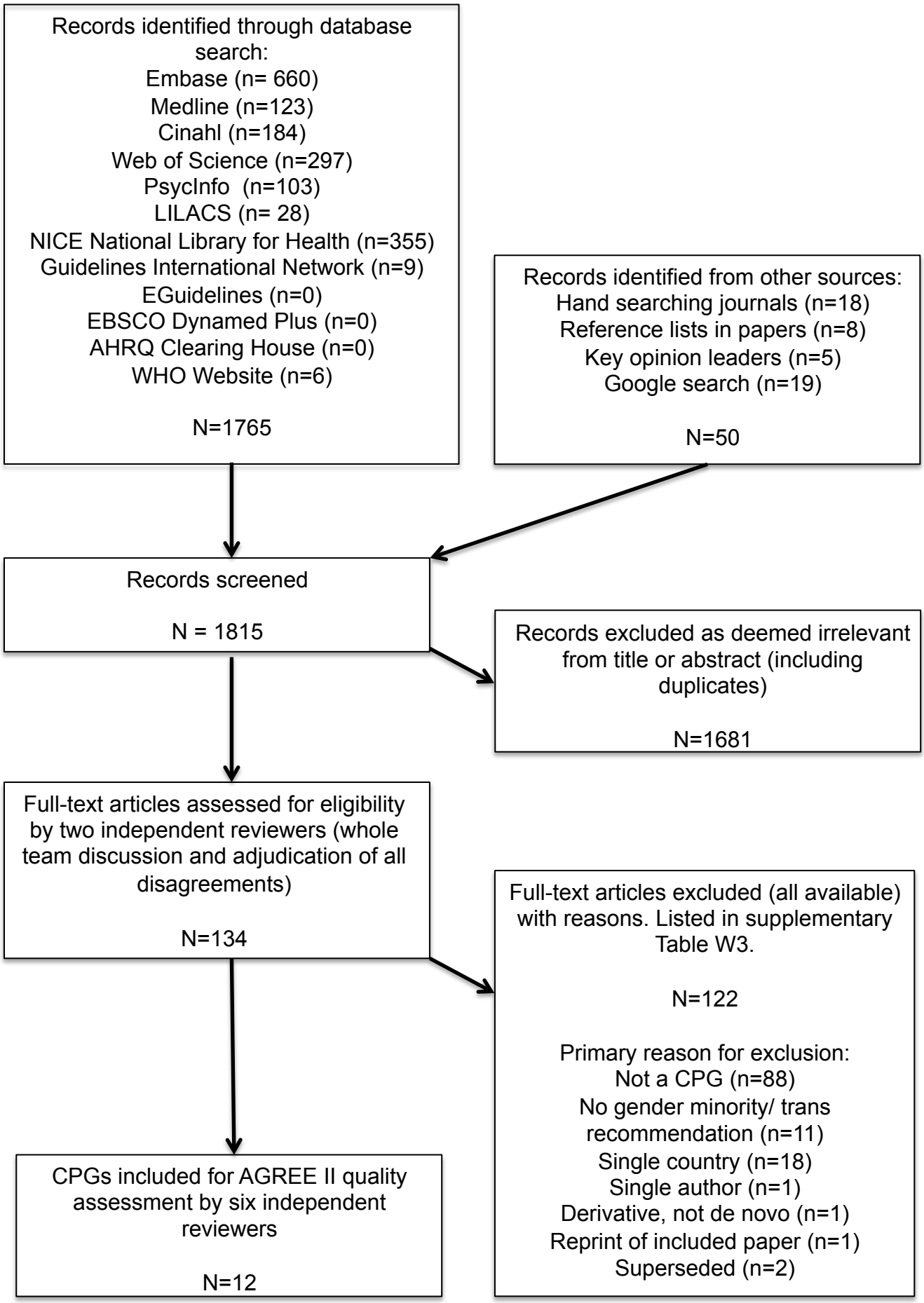
86 Harding Center for Risk Literacy. Fact boxes. https://www.hardingcenter.de/en/fact-boxes (accessed 8 Jul 2020).

87 Winton Centre for Risk and Evidence Communication. https://wintoncentre.maths.cam.ac.uk/ (accessed 8 Jul 2020).

Legend/Key for Figure

Figure 1. PRISMA flow diagram

Key: CPG, clinical practice guideline; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses


Records identified through database search:
Embase (n= 660)
Medline (n=123)
Cinahl (n=184)
Web of Science (n=297)
PsycInfo (n=103)
LILACS (n= 28)
NICE National Library for Health (n=355)
Guidelines International Network (n=9)
EGuidelines (n=0)
EBSCO Dynamed Plus (n=0)
AHRQ Clearing House (n=0)
WHO Website (n=6)
N=1765
Records identified from other sources:
Hand searching journals (n=18)
Reference lists in papers (n=8)
Key opinion leaders (n=5)
Google search (n=19)
N=50
Records screened
N = 1815
Records excluded as deemed irrelevant from title or abstract (including duplicates)
N=1681
Full-text articles assessed for eligibility by two independent reviewers (whole team discussion and adjudication of all disagreements)
N=134
Full-text articles excluded (all available) with reasons. Listed in supplementary Table W3.
N=122
Primary reason for exclusion:
Not a CPG (n=88)
No gender minority/ trans recommendation (n=11)
Single country (n=18)
Single author (n=1)
Derivative, not de novo (n=1)
Reprint of included paper (n=1)
Superseded (n=2)
CPGs included for AGREE II quality assessment by six independent reviewers
N=12

International Clinical Practice Guidelines for Gender Minority/Trans People: Systematic Review and Quality Assessment

Supplementary/ Web/ Appendices

W1. Search terms used and search strategy for at least one database

W2. Stakeholder and review team priority scoring exercise

W3. Full text excluded studies with reasons for exclusion

W4. Extracted sentences relating to mortality or quality of life with associated references from Clinical Practice Guidelines

W5. Extracted key recommendations from Clinical Practice Guidelines

W1: Literature searching – Databases searched and search terms used

Embase <1974 to 2019 July 29>

1 transgender.mp. or transgender/ (7297)
2 transsexual.mp. (2070)
3 gender identity/ or gender non-conforming.mp. (15929)
4 non-binary.mp. (219)
5 gender minority.mp. or "sexual and gender minority"/ (1582)
6 transman.mp. (20)
7 transwoman.mp. (25)
8 gender dysphoria.mp. or gender dysphoria/ (1887)
9 gender diversity.mp. (257)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (24836)
11 practice guideline/ or clinical guideline.mp. (387400)
12 10 and 11 (511)
13 limit 12 to yr="2008 - 2020" (460)

Ovid MEDLINE(R) ALL <1946 to July 29, 2019>

1 gender diversity.mp. (225)
2 gender dysphoria.mp. or Transsexualism/ or Gender Dysphoria/ or Gender Identity/ (20817)
3 gender minority.mp. or "Sexual and Gender Minorities"/ (2406)
4 Transgender Persons/ or gender non-conforming.mp. (2429)
5 non-binary.mp. (164)
6 transgender.mp. (5364)
7 transman.mp. (8)
8 transwoman.mp. (13)
9 Transsexualism/ or transsexual.mp. (3855)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (26619)
11 Practice Guidelines as Topic/ or clinical guideline.mp. (112006)
12 10 and 11 (103)

Web of Science

Search terms: (TOPIC: (((((transgender OR gender dysphoria) OR transsexual) OR gender identity) OR transman) OR transwomen) AND TOPIC: (clinical guideline OR practice guideline)) [271 results]

(TOPIC: (gender incongruence) AND TOPIC: (clinical guideline OR practice guideline))

NICE Evidence

Search terms: Transgender, gender dysphoria

CINAHL
(transgender or transsexual or transsexual or gender variant or gender non-conforming or transmen or transwomen or gender dysphoria or gender identity) AND (clinical guideline or practice guideline)

PSYCInfo
(transgender or transsexual or transexual or gender variant or gender non-conforming or transmen or transwomen or gender dysphoria or gender identity) AND (clinical guideline or practice guideline)

AHRQ National Guidelines Clearing House
Search terms: trans, gender identity. Was stopped in 2018 – no update searches available

eGuidelines
Search terms: trans, gender identity

Guidelines International Network
Search terms: Transgender, gender dysphoria, gender identity

WHO website – not searchable on so used Google instead

Google Search terms: WHO transgender guidelines - First 100 hits examined

Update: WHO transgender guidelines 2020

LILACS
Search term: gender dysphoria

W2: Stakeholder prioritisation exercise and comparison with research team

Domains	Stakeholders (n=19) #						Reviewers (n=6)					
Priority	**1 highest**	**2**	**3**	**4**	**5**	**6 lowest**	**1 highest**	**2**	**3**	**4**	**5**	**6 lowest**
Scope and purpose	***	***** *	*	**	***** *		*	*	*****	**		*
Stakeholder Involvement	***** ****	*	***	**	**	*			*	*	**	*
Rigour of development	*	*	*****	*****	****	**	*****	*				
Clarity and presentation	***	***	*****	***	*	***		*		***	*	
Applicability	*	***** **	**	*****	***			*			*	***
Editorial independence	**	*	**	*		***** ***** *		**			**	*

Key: # Numbers do not all add up to 19 as one stakeholder only gave first two preferences; * stakeholder or reviewer preference vote. Green shows highest priority and red shows lowest priority

W3: Excluded full studies with reasons for exclusion

Full Citation (n=122)	Reason(s) for exclusion
Ackerley CG, Poteat T, Kelley CF. Human Immunodeficiency Virus in Transgender Persons. *Endocrinol Metab Clin North Am* 2019;**48**:453–64. doi:10.1016/j.ecl.2019.02.007	Not a CPG. Single country.
Adams N, Pearce R, Veale J, *et al.* Guidance and Ethical Considerations for Undertaking Transgender Health Research and Institutional Review Boards Adjudicating this Research. *Transgender Heal* 2017;**2**:165–75. doi:10.1089/trgh.2017.0012	Not a CPG.
ADFAM. Including diverse families: good practice guidelines. 2010. https://adfam.org.uk/files/docs/idf_toolkit.pdf	No TG specific recommendation. Single country.
Akl EA, Kennedy C, Konda K, *et al.* Using GRADE methodology for the development of public health guidelines for the prevention and treatment of HIV and other STIs among men who have sex with men and transgender people. *BMC Public Health* 2012;**12**:386. doi:10.1186/1471-2458-12-386	Not a CPG.
American College of Obstetricians and Gynecologists, Sokkary N, Gomez-Lobo V. Committee Opinion No. 685: Care for Transgender Adolescents. *Obstet Gynecol* 2017;**129**:e11–6. doi:10.1097/AOG.0000000000001861	Not a CPG. Single country.
American Psychological Assoc. Guidelines for psychological practice with transgender and gender nonconforming people. *Am Psychol* 2015;**70**:832–64. doi:10.1037/a0039906	Single country.
American Psychological Association. Multicultural guidelines: An ecological approach to context, identity, and intersectionality, 2017. *Am Psychol Assoc*: 2017.http://www.apa.org/about/policy/multicultural-guidelines.pdf	Single country.
American Society for Reproductive Medicine, American College of Obstetricians and Gynecologists. Prepregnancy counseling: Committee Opinion No. 762. *Fertil Steril* 2019;**111**:32–42. doi:10.1016/j.fertnstert.2018.12.003	Not a CPG. No TG specific recommendation. Single country.
Baggaley R, Armstrong A, Dodd Z, *et al.* Young key populations and HIV: A special emphasis and consideration in the new WHO Consolidated Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations. *J Int AIDS Soc* 2015;**18**:85–8. doi:10.7448/IAS.18.2.19438	Not a CPG.
Barrett J. Gender Dysphoria in Adults. BMJ Best Pract. 2018.https://bestpractice.bmj.com/topics/en-gb/992	Not a CPG. Single author.
Bekker L-G, Rebe K, Venter F, *et al.* Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV-1 infection. *South Afr J HIV Med* 2016;**17**. doi:10.4102/sajhivmed.v17i1.455	Single country.
Berli JU, Capitán L, Simon D, *et al.* Facial gender confirmation surgery—review of the literature and recommendations for Version 8 of the WPATH Standards of Care. *Int J Transgenderism* 2017;**18**:264–70. doi:10.1080/15532739.2017.1302862	Not a CPG.
Bhugra D, Gupta S, Schouler-Ocak M, *et al.* EPA Guidance Mental Health Care of Migrants. *Eur Psychiatry* 2014;**29**:107–15. doi:10.1016/j.eurpsy.2014.01.003	Not a CPG. No TG specific recommendation.
Bonifacio JH, Maser C, Stadelman K, *et al.* Management of gender dysphoria in adolescents in primary care. *Can Med Assoc J* 2019;**191**:E69–75. doi:10.1503/cmaj.180672	Not a CPG. Single country.
Bonnington A, Dianat S, Kerns J, *et al.* Society of Family Planning clinical recommendations: Contraceptive counseling for transgender and gender diverse people who were female sex assigned at birth. *Contraception* Published Online First: 2020. doi:10.1016/j.contraception.2020.04.001	Single country.
Boroughs MS, Bedoya CA, O'Cleirigh C, *et al.* Toward Defining, Measuring, and Evaluating LGBT Cultural Competence for Psychologists. *Clin Psychol Sci Pract* 2015;**22**:151–71. doi:10.1111/cpsp.12098	Not a CPG. Single country.
Bourjeily G, Mehta S. Gender diversity in Obstetric Medicine. *Obstet Med* 2019;**12**:55–6. doi:10.1177/1753495X19851711	Not a CPG.
Brown B, Poteat T, Marg L, *et al.* Human Papillomavirus-Related Cancer Surveillance, Prevention, and Screening among Transgender Men and Women: Neglected Populations at High Risk. *LGBT Heal* 2017;**4**:315–9. doi:10.1089/lgbt.2016.0142	Not a CPG.
Brown GR. Recommended revisions to the world professional association for transgender health's standards of care section on medical care for incarcerated persons with gender identity disorder. *Int J Transgenderism* 2009;**11**:133–9. doi:10.1080/15532730903008073	Not a CPG. Single author.
Bruessow DM, O'Connor LM, Eaman E, *et al.* Transgender Patients: Considerations for the Family Physician. *Fam Dr A J New York State Acad Fam Physicians* 2019;**7**:36–41.	Not a CPG. Single country.

Burns ZT, Bitterman DS, Liu KX, *et al.* Towards a standard of care in oncology for transgender patients. *Lancet Oncol* 2019;**20**:331–3. doi:10.1016/S1470-2045(18)30942-2	Not a CPG. Single country.
Byne W, Bradley SJ, Coleman E, *et al.* Treatment of gender identity disorder. *Am J Psychiatry* 2012;**169**:875–6. doi:10.1176/appi.ajp.2012.169.8.875	Not a CPG.
Canady V. APA practice guidelines for females focus on their strength, resilience. *Ment Heal Wkly* 2019;**29**:1–8. doi:10.1002/mhw	Not a CPG. Single Country. Single author.
Capitán L, Gutiérrez Santamaría J, Simon D, *et al.* Facial Gender Confirmation Surgery. *Plast Reconstr Surg* 2020;**145**:818e-828e. doi:10.1097/PRS.0000000000006686	Not a CPG. Single Country.
Carswell JM, Roberts SA. Induction and Maintenance of Amenorrhea in Transmasculine and Nonbinary Adolescents. *Transgender Heal* 2017;**2**:195–201. doi:10.1089/trgh.2017.0021	Not a CPG. Single country.
Chen D, Hidalgo MA, Leibowitz S, *et al.* Multidisciplinary Care for Gender-Diverse Youth: A Narrative Review and Unique Model of Gender-Affirming Care. *Transgender Heal* 2016;**1**:117–23. doi:10.1089/trgh.2016.0009	Not a CPG.
Church of England. *Valuing All God's Children: Challenging homophobic, biphobic and transphobic bullying*. 2nd ed. Church of England Education Office 2019. https://www.churchofengland.org/sites/default/files/2019-07/Valuing All God%27s Children July 2019_0.pdf	Not a CPG.
Cohen J, Lo YR, Caceres CF, *et al.* WHO guidelines for HIV/STI prevention and care among MSM and transgender people: Implications for policy and practice. *Sex Transm Infect* 2013;**89**:536–8. doi:10.1136/sextrans-2013-051121	Not a CPG.
Cohen-Kettenis PT, Klink D. Adolescents with gender dysphoria. *Best Pract Res Clin Endocrinol Metab* 2015;**29**:485–95. doi:10.1016/j.beem.2015.01.004	Not a CPG.
Colebunders B, De Cuypere G, Monstrey S. New Criteria for Sex Reassignment Surgery: WPATH Standards of Care, Version 7, Revisited. *Int J Transgenderism* 2015;**16**:222–33. doi:10.1080/15532739.2015.1081086	Not a CPG.
Coxon J, Seal L. Hormone management of trans men. *Trends Urol Men's Heal* 2018;**9**:8–12. doi:10.1002/tre.651	Not a CPG. Single country.
D'Angelo A, Panayotidis C, Amso N, *et al.* Recommendations for good practice in ultrasound: oocyte pick up†. *Hum Reprod Open* 2019;**2019**:1689–99. doi:10.1093/hropen/hoz025	Not a CPG. No TG specific recommendation.
Dahl M, Feldman JL, Goldberg J, *et al.* Endocrine Therapy for Transgender Adults in British Columbia: Suggested Guidelines Physical Aspects of Transgender Endocrine Therapy. 2015. http://www.phsa.ca/transcarebc/Documents/HealthProf/BC-Trans-Adult-Endocrine-Guidelines-2015.pdf	Single country.
Davies S. The Evidence Behind the Practice: A Review of WPATH Suggested Guidelines in Transgender Voice and Communication. *Perspect ASHA Spec Interes Groups* 2017;**2**:64–73. doi:10.1044/persp2.SIG10.64	Single author.
De Antonio IE, Gómez-Gil E. Coordination of healthcare for transsexual persons: A multidisciplinary approach. *Curr Opin Endocrinol Diabetes Obes* 2013;**20**:585–91. doi:10.1097/01.med.0000436182.42966.31	Not a CPG.
de Haan G, Santos G-M, Arayasirikul S, *et al.* Non-Prescribed Hormone Use and Barriers to Care for Transgender Women in San Francisco. *LGBT Heal* 2015;**2**:313–23. doi:10.1089/lgbt.2014.0128	Not a CPG.
de Vries ALC, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: The Dutch approach. *J Homosex* 2012;**59**:301–20. doi:10.1080/00918369.2012.653300	Not a CPG.
Dèttore D, Ristori J, Antonelli P, *et al.* Gender dysphoria in adolescents: The need for a shared assessment protocol and proposal of the AGIR protocol. *J Psychopathol* 2015;**21**:152–8.	Not a CPG.
Deutsch MB, Green J, Keatley JA, *et al.* Electronic medical records and the transgender patient: Recommendations from the world professional association for Transgender Health EMR working group. *J Am Med Informatics Assoc* 2013;**20**:700–3. doi:10.1136/amiajnl-2012-001472	Not a CPG. Single country.
Devon Partnership NHS Trust. PG12 Pharmacological Treatment of Gender Dysphoria. 2015.https://www.gires.org.uk/wp-content/uploads/2014/08/PG12-GenderDysphoria.pdf	Single country.
Etienne Tollinche L, Burrows Walters C, Radix A, *et al.* The perioperative care of the transgender patient. *Anesth Analg* 2018;**127**:359–66. doi:10.1213/ANE.0000000000003371	Not a CPG. Single country.
European Society of Human Genetics. Genetic testing in asymptomatic minors: Recommendations of the European Society of Human Genetics. *Eur J Hum Genet* 2009;**17**:720–1. doi:10.1038/ejhg.2009.26	No TG specific recommendation. Single author.

Finlayson C, Johnson EK, Chen D, *et al.* Proceedings of the Working Group Session on Fertility Preservation for Individuals with Gender and Sex Diversity. *Transgender Heal* 2016;**1**:99–107. doi:10.1089/trgh.2016.0008	Not a CPG.
Fisher CB, Fried AL, Desmond M, *et al.* Perceived barriers to HIV prevention services for transgender youth. *LGBT Heal* 2018;**5**:350–8. doi:10.1089/lgbt.2017.0098	Not a CPG.
Francis C, Grober E, Potter E, *et al.* A Simple Guide for Simple Orchiectomy in Transition-Related Surgeries. *Sex Med Rev* 2020:3–7. doi:10.1016/j.sxmr.2019.11.004	Not a CPG. Single country.
Fraser L. Psychotherapy in the world professional association for transgender health's standards of care: Background and recommendations. *Int J Transgenderism* 2009;**11**:110–26. doi:10.1080/15532730903008057	Not a CPG. Single author.
Gamble RM, Taylor SS, Huggins AD, *et al.* Trans-specific Geriatric Health Assessment (TGHA): An inclusive clinical guideline for the geriatric transgender patient in a primary care setting. *Maturitas* 2020;**132**:70–5. doi:10.1016/j.maturitas.2019.12.005	Not a CPG. Single country.
GIRES. Guidance for GPs , other clinicians and health professionals on the care of gender variant people Transgender wellbeing and healthcare. UK Dep. Heal. 2008.https://midessexccg.nhs.uk/medicines-optimisation/clinical-pathways-and-medication-guidelines/chapter-6-endocrine-system-2/1142-guidance-for-gps-and-hormone-treatment-for-gender-dysphoria-1/file	Single country. Out of date.
Goeckenjan M, Glaß K, Torka S, *et al.* Indications for fertility preservation. *Gynakologische Endokrinol* 2019;:71–7. doi:10.1007/s10304-019-0241-3	Not a CPG. Single country.
Griffith C, Akers W, Dispenza F, *et al.* Standards of Care for Research with Participants Who Identify as LGBTQ+. *J LGBT Issues Couns* 2017;**11**:212–29. doi:10.1080/15538605.2017.1380549	Not a CPG. Single country
Guidance on Gender Dysphoria for Nurses. *Nurs Stand* 2013;**28**:10. doi:10.7748/ns2013.10.28.9.10.s10	Not a CPG.
Hagen DB, Galupo MP. Trans* Individuals' Experiences of Gendered Language with Health Care Providers: Recommendations for Practitioners. *Int J Transgenderism* 2014;**15**:16–34. doi:10.1080/15532739.2014.890560	Not a CPG.
Hamidi O, Davidge-Pitts CJ. Transfeminine Hormone Therapy. *Endocrinol Metab Clin North Am* 2019;**48**:341–55. doi:10.1016/j.ecl.2019.02.001	Not a CPG. Single country.
Health Policy Project, Asia Pacific Transgender Network, United Nations Development Programme. *Blueprint for the provision of comprehensive care for trans people and trans communities in Asia and the Pacific*. Washington, DC: Futures Group, Health Policy Project 2015. http://www.asia-pacific.undp.org/content/rbap/en/home/library/democratic_governance/hiv_aids/blueprint-for-the-provision-of-comprehensive-care-for-trans-peop/	Not a CPG.
Heidari S, Babor TF, De Castro P, *et al.* Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use. *Res Integr Peer Rev* 2016;**1**:1–9. doi:10.1186/s41073-016-0007-6	Not a CPG.
Hembree W, Cohen-Kettenis P, Gooren L, *et al.* Endocrine treatment of gender-dysphoric/ gender-incongruent persons: an endocrine society clinical practice guideline. *Endocr Pract* 2017;**23**:1437–71.	Reprint of included paper (fully cited).
Hirsch S, Pickering J, Adler R. Meeting the Needs of Trans and Gender Diverse Youth: The Varied, Ubiquitous Role of the Speech-Language Pathologist in Voice and Communication Therapy/Training. *Perspect ASHA Spec Interes Groups* 2019;**4**:111–7. doi:10.1044/2018_PERS-SIG3-2018-0016	Not a CPG. Single country.
House H, Gaines S, Hawkins LA. Sexual and Gender Minority Adolescents: Meeting the Needs of Our LGBTQ Patients and Their Families. *Clin Pediatr Emerg Med* 2019;**20**:9–16. doi:10.1016/j.cpem.2019.02.004	Not a CPG. Single country.
Hughes LD, Berzin OKG, Leung M, *et al.* Adapting Healthcare Quality Measures to Transgender Individuals. *LGBT Heal* 2017;**4**:248–51. doi:10.1089/lgbt.2017.0009	Not a CPG. Single country.
Human Rights Campaign, American Academy of Pediatrics, American College of Osteopathic Pediatricians. Supporting & Caring for Transgender Children. 2016.http://hrc.im/supportingtranschildren	Not a CPG. Single country.
IAPAC. IAPAC Protocols for the Integrated Management of HIV and Noncommunicable Diseases. *Int Assoc Provid AIDS care* Published Online First: 2018.https://www.iapac.org/files/2018/07/IAPAC-Protocols-for-the-Integrated-Management-of-HIV-and-Noncommunicable-Diseases_3.pdf	No TG specific recommendation.
IMAP. IMAP Statement on hormone therapy for transgender people. Published Online First: 2015. https://www.ippf.org/sites/default/files/ippf_imap_transgender.pdf	Not a CPG.
In Case You Haven't Heard. *Mental Health Weekly* 2015;**25**:8-8. doi:10.1002/mhw.30307	Not a CPG.
International Association for the Study of Pain. *Guide to Pain Management in Low-Resource Settings*. Seattle: : IASP 2010. https://ebooks.iasp-	Not a CPG. No TG specific

pain.org/guide_to_pain_management_in_low_resource_settings	recommendation.
International Association of Physicians in AIDS Care. IAPAC – Blueprint to Address the Sexual and Reproductive Health Care and STI/HIV Prevention Needs of Adolescent Girls and Young Women. Published Online First: 2011.https://www.iapac.org/guidance/recommendations/blueprint-to-address-the-sexual-and-reproductive-health-care-and-sti-hiv-prevention-needs-of-adolescent-girls-and-young-women-in-latin-america-and-the-caribbean/	No TG specific recommendation.
International Association of Providers in AIDS Care. Recommendations for the rapid expansion of HIV self-testing in Fast-Track Cities. Published Online First: 2017.http://www.iapac.org/uploads/IAPAC-ASLM-HIVST-FTC-Recommendations-012617.pdf	No TG specific recommendation.
International Planned Parenthood Federation. IPPF. Hormonal contraception: recommendations for women at high risk of HIV. Published Online First: 2017.http://www.ippf.org/sites/default/files/2017-07/ippf_technical_brief_HC_HIV_June2017.pdf	Not a CPG. No TG specific recommendation.
International Planned Parenthood Federation. Putting sexuality back into Comprehensive Sexuality Education: making the case for a rights-based, sex-positive approach. Published Online First: 2016.https://www.ippf.org/sites/default/files/2016-10/Putting Sexuality back into Comprehensive Sexuality Education_0.pdf	Not a CPG. No TG specific recommendation.
Jungwirth, A; Diemer, T; Kopa, Z; Krausz, C; Minhas, S; Tournaye H. *EAU Guidelines on Male Infertility*. European Association of Urology 2018.	Superseded by 2020 CPG with no TG recommendations
Kaltiala-Heino R, Bergman H, Työläjärvi M, *et al.* Gender dysphoria in adolescence: current perspectives. *Adolesc Health Med Ther* 2018; **9**:31–41. doi:10.2147/AHMT.S135432	Not a CPG.
Karasic DH, Fraser L. Multidisciplinary Care and the Standards of Care for Transgender and Gender Nonconforming Individuals. *Clin Plast Surg* 2018;**45**:295–9. doi:10.1016/j.cps.2018.03.016	Derivative, not de novo.
Kemp K, Dibley L, Chauhan U, *et al.* Second N-ECCO Consensus Statements on the European Nursing Roles in Caring for Patients with Crohn's Disease or Ulcerative Colitis. *J Crohn's Colitis* 2018;**12**:760–76. doi:10.1093/ecco-jcc/jjy020	No TG specific recommendation.
Khosla S, Davidge-Pitts C. Skeletal considerations in the medical treatment of transgender people. *Lancet Diabetes Endocrinol* 2019;**7**:893–5. doi:10.1016/S2213-8587(19)30353-5	Not a CPG.
Klein DA, Malcolm NM, Berry-Bibee EN, et al. Quality Primary Care and Family Planning Services for LGBT Clients: A Comprehensive Review of Clinical Guidelines. *LGBT Health*. 2018;**5**:153-170. Doi:10.1089/lgbt.2017.0213	Not a CPG. No TG specific recommendation. Derivative, not de novo. Single country.
Klein M, Sathasivam A, Novoa Y, *et al.* Recent Consensus Statements in Pediatric Endocrinology: A Selective Review. *Pediatr Clin North Am* 2011;**58**:1301–15. doi:10.1016/j.pcl.2011.07.014	Not CPG. Derivative not de novo. No TG specific recommendation.
LGBT Health Program. *Guidelines and Protocols for Hormone Therapy and Primary Health Care for Trans Clients*. Toronto: Sherbourne Health Centre 2015. http://sherbourne.on.ca/lgbt-health/guidelines-protocols-for-trans-care/	Single country. Single author.
MacDonald S, Smith S. Dermatologists guide to cultural competency and the LGBTIQ patient. *Australas J Dermatol* 2018;**59**:85.	Not a CPG.
Martinez C, Rikhi R, Haque T, *et al.* Gender Identity, Hormone Therapy, and Cardiovascular Disease Risk. *Curr Probl Cardiol* 2020;**45**. doi:10.1016/j.cpcardiol.2018.09.003	Not a CPG.
Meyenburg B, Korte A, Moller B, *et al.* Gender identity disorders in childhood and adolescence (F64) / Storungen der Geschlechtsidentitat im Kindes- und Jugendalter (F64). *Prax Kinderpsychol Kinderpsychiatr* 2014;**63**:542–52.	Not a CPG.
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World Health Organization. *Preventing Suicide A Community Engagement Toolkit*. 2018. https://apps.who.int/iris/bitstream/handle/10665/272860/9789241513791-eng.pdf	Not a CPG. No TG specific recommendation.
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Key: CPG = clinical practice guideline; TG = trans people/gender minority

W4: Extracted sentences relating to mortality or quality of life with associated references from Clinical Practice Guidelines

	Author (yr)	In-text statement on Mortality/ Quality of Life (QoL)	Page	References
1	Coleman et al. (2012)	**Mortality:** Two long-term observational studies, both retrospective, compared the mortality & psychiatric morbidity of transsexual adults to those of general population samples (Asscheman et al., 2011; Dhejne et al., 2011). An analysis of data from the Swedish National Board of Health & Welfare information registry found that individuals who had received sex reassignment surgery (191 MtF & 133 FtM) had significantly higher rates of mortality, suicide, suicidal behavior, & psychiatric morbidity than those for a nontranssexual control group matched on age, immigrant status, prior psychiatric morbidity, & birth sex (Dhejne et al., 2011). Similarly, a study in the Netherlands reported a higher total mortality rate, including incidence of suicide, in both pre- & post-surgery transsexual patients (966 MtF and 365 MtF) than in the general population of that country (Asscheman et al., 2011). Neither of these studies questioned the efficacy of sex reassignment; indeed, both lacked an adequate comparison group of transsexuals who either did not receive treatment or who received treatment other than genital surgery. Moreover, transsexual people in these studies were treated as far back as the 1970s. However, these findings do emphasize the need to have good long-term psychological & psychiatric care available for this population. More studies are needed that focus on the outcomes of current assessment & treatment approaches for gender dysphoria.	108	Asscheman H, Giltay EJ, Megens JAJ, *et al.* A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol* 2011;**164**:635–42. doi:10.1530/EJE-10-1038 Dhejne C, Lichtenstein P, Boman M, *et al.* Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden. *PLoS One* 2011;**6**:e16885. doi:10.1371/journal.pone.0016885
		QoL: One troubling report (Newfield et al., 2006) documented lower scores on QoL (measured with the SF-36) for FtM patients than for the general population. A weakness of that study is that it recruited its 384 participants by a general email rather than a systematic approach, and the degree and type of treatment were not recorded. Study participants who were taking testosterone had typically being doing so for less than 5 years. Reported QoL qas higher for patients who had undergone breast/chest surgery than for those who had not (p<.001). (A similar analysis was not done for genital surgery.)	108	Newfield E, Hart S, Dibble S, *et al.* Female-to-male transgender quality of life. *Qual Life Res* 2006;**15**:1447–57. doi:10.1007/s11136-006-0002-3
		QoL: In other work, Kuhn & colleagues (2009) used the King's Health Questionnaire to assess the quality of life of 55 transsexual patients at 15 years after surgery. Scores were compared to those of 20 healthy female control patients who had undergone abdominal/pelvic surgery in the past. Quality of life scores for transsexual patients were the same or better than those of control patients for some subscales (emotions, sleep, incontinence, symptom severity, and role limitation), but worse in other domains (general health, physical limitation, and personal limitation).	108	Kuhn A, Bodmer C, Stadlmayr W, *et al.* Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertil Steril* 2009;**92**:1685-1689.e3. doi:10.1016/j.fertnstert.2008.08.126
2	Davies et al. (2015)	**QoL:** A number of studies indicate that speech-therapy intervention is useful in helping gender nonconforming individuals portray their gender identity through speech (Carew, Dacakis, & Oates, 2007; Dacakis, Oates, & Douglas, 2012; Gelfer & Tice, 2013; Hancock & Garabedian, 2013; Meszaros et al., 2005). Such changes to communication are not simply superficial; they can reduce gender dysphoria and improve mental health and quality of life.	117-118	Carew L, Dacakis G, Oates J. The Effectiveness of Oral Resonance Therapy on the Perception of Femininity of Voice in Male-to-Female Transsexuals. *J Voice* 2007;**21**:591–603. doi:10.1016/j.jvoice.2006.05.005 Dacakis G, Oates J, Douglas J. Beyond voice. *Curr Opin*

				Otolaryngol Head Neck Surg 2012;**20**:165–70. doi:10.1097/MOO.0b013e3283530f85 Gelfer MP, Tice RM. Perceptual and Acoustic Outcomes of Voice Therapy for Male-to-Female Transgender Individuals Immediately After Therapy and 15 Months Later. *J Voice* 2013;**27**:335–47. doi:10.1016/j.jvoice.2012.07.009 Hancock AB, Garabedian LM. Transgender voice and communication treatment: a retrospective chart review of 25 cases. *Int J Lang Commun Disord* 2013;**48**:54–65. doi:10.1111/j.1460-6984.2012.00185.x Mészáros K, Csokonai Vitéz L, Szabolcs I, *et al.* Efficacy of Conservative Voice Treatment in Male-to-Female Transsexuals. *Folia Phoniatr Logop* 2005;**57**:111–8. doi:10.1159/000083572 * Hancock AB, Krissinger J, Owen K. Voice Perceptions and Quality of Life of Transgender People. *J Voice* 2011;**25**:553–8. doi:10.1016/j.jvoice.2010.07.013
3	ECDC (2018)	**Mortality:** the World Health Organization (WHO) and UNAIDS have identified several targets along the continuum of care for hepatitis B virus (HBV), hepatitis C virus (HCV) and HIV. These *include* promoting early diagnosis, scaling up treatment and reducing disease-related mortality [12,13].	3	12. World Health Organization. Global health sector strategy on viral hepatitis 2016–2021: towards ending viral hepatitis. Geneva: WHO; 2016. 13. World Health Organization. Global health sector strategy on HIV, 2016–2021: towards ending AIDS. Geneva: WHO; 2016.
		QoL (as QALY): Since then, the feasibility of birth cohort testing for HCV has been studied in several European countries, including Ireland, Italy, and Spain [87–89]. In the studies in Ireland and Spain, the authors concluded that to effectively implement birth cohort testing for HCV, each country must determine its own HCV seroprevalence by year in order to successfully develop screening recommendations because risk factors, particularly injecting drug use, can affect the selection of birth cohort. In Italy, authors found that the anti-HCV screening program had an acceptable expenditure increase for the National Health Service compared to the cost per quality-adjusted life year (QALY) of other approved interventions or treatments in Italy."	18	87. Group HCSGD. Background to recommendation 20: general population or birth cohort screening. Dublin: Health Protection Surveillance Centre; 2017. 88. Ruggeri M, Coretti S, Gasbarrini A, Cicchetti A. Economic assessment of an anti-HCV screening program in Italy. Value Health. 2013;16(6):965–72. 89. Mena A, Moldes L, Meijide H, Canizares A, Castro-Iglesias A, Delgado M, et al. Seroprevalence of HCV and HIV infections by year of birth in Spain: impact of US CDC and USPSTF recommendations for HCV and HIV testing. PLoS ONE. 2014;9(12):e113062.
		QALY: Four cost implication studies of HIV testing in hospital settings have been conducted in UK. They show that universal offer testing was highly cost effective if future healthcare costs & QALYs are incorporated into calculations [236-239]	23	236. Ong KJ, Thornton AC, Fisher M, Hutt R, Nicholson S, Palfreeman A, et al. Estimated cost per HIV infection diagnosed through routine HIV testing offered in acute general medical admission units and general practice settings in England. HIV Medicine. 2016;17(4):247-54. 237. Pizzo E, Rayment M, Thornton A, Rae C, Hartney T, Delpech V, et al. Cost-effectiveness analysis of HIV testing in non-traditional settings-the HINTS study. HIV Medicine. 2014;15:93. 238. Sewell J, Capocci S, Johnson J, Solamalai A, Hopkins S, Cropley I, et al. Expanded blood borne virus testing in a

				tuberculosis clinic. A cost and yield analysis. J Infect. 2015;70(4):317-23. 239. Alexander H, Brady M, Poulton M. A calculation of the financial impact of opt-out HIV testing in a London Emergency Department (ED). HIV Med. 2016 April.
4	Gilligan et al. (2017)	**Mortality/QoL:** no statements linked to references		
5	Hembree et al. (2017)	**Mortality:** Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (161). … The largest cohort of transgender females (mean age 41 years, followed for a mean of 10 years) showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (161).	3891	161. van Kesteren PJM, Asscheman H, Megens JAJ, Gooren LJG. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf). 1997;47(3): 337–343.
		Mortality: A systematic review of the literature found that data were insufficient (due to very low–quality evidence) to allow a meaningful assessment of patient-important outcomes, such as death, stroke, myocardial infarction, or VTE in transgender males (176). Future research is needed to ascertain the potential harm of hormonal therapies (176).	3895	176. Elamin MB, Garcia MZ, Murad MH, Erwin PJ, Montori VM. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. Clin Endocrinol (Oxf). 2010;72(1):1–10.
		Mortality: Another analysis demonstrated that, despite the young average age at death following surgery and the relatively larger number of individuals with somatic morbidity, the study does not allow for determination of causal relationships between, for example, specific types of hormonal or surgical treatment received and somatic morbidity and mortality (263).	3895	**263. Djordjevic ML, Bizic MR, Duisin D, Bouman MB, Buncamper M. Reversal Surgery in regretful male-to-female transsexuals after sex reassignment surgery. J Sex Med. 2016;13(6):1000–1007. *Note title of reference 262:* *262. Simonsen RK, Hald GM, Kristensen E, Giraldi A. Long-term follow-up of individuals undergoing sex-reassignment surgery: somatic morbidity and cause of death. Sex Med. 2016;4(1): e60–e68.*
		QoL: Likewise, a meta-analysis of 19 randomized trials in nontransgender males on testosterone replacement showed no increased incidence of cardiovascular events (185).	3891	185. Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, Bhasin S. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci. 2005;60(11):1451–1457.
6	IAPHCCO (2015)	**Mortality:** The Strategic Timing of AntiRetroviral Treatment (START) study recently showed a 53% reduction in serious morbidity and mortality from HIV due to early ART at CD4 counts of over 500 cells/mm3 (96)	6	96. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373(9):795–807.
		Mortality Increasing early access to ART is associated with decreased AIDS-related morbidity and mortality, as well as reduced risk of HIV transmission (167)	8	167. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. Lancet Infect Dis. 2014;14(4):281–290.
		Mortality: Antiretroviral therapy is proven to prevent HIV-related morbidity, mortality, and transmission.(7)	9	7. Montaner JS, Lima VD, Harrigan PR, et al. Expansion of HAART coverage is associated with sustained decreases in HIV/AIDS morbidity, mortality and HIV transmission: the ‘‘HIV Treatment as Prevention’’ experience in a Canadian setting. PLoS One. 2014; 9(2):e87872.

		Mortality: Community-located ART distribution is a cost-effective service delivery model whose rates of attrition and mortality are similar to those at the facility level. (195,196)	10	195. Kredo T, Ford N, Adeniyi FB, Garner P. Decentralising HIV treatment in lower- and middle-income countries. Cochrane Database Syst Rev. 2013;6:CD009987. 196. Chu C, Umanski G, Blank A, Grossberg R, Selwyn PA. HIVinfected patients and treatment outcomes: an equivalence study of community-located, primary care-based HIV treatment vs. hospital-based specialty care in the Bronx, New York. AIDS Care. 2010;22(12):1522–1529.
		Mortality In Uganda, ART distribution at community-based sites was found to be associated with significantly higher rates of retention in care and lower mortality rates. (88, 204)	10	88. Wamboga Magawa J, Mpiima D. Community ART Delivery Model for High Retention of Patients on Antiretroviral Therapy: The AIDS Support Organisation (TASO) Operational Research Findings East and Central Uganda, Resource-Limited Setting. Presented at: 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention; June 30-July 3, 2013; Kuala Lumpur, Malaysia. 204. Grimsrud A, Patten G, Sharp J, Myer L, Wilkinson L, Bekker LG. Extending dispensing intervals for stable patients on ART. J Acquir Immune Defic Syndr. 2014;66(2):e58–e60.
		Mortality /QoL: Today, a person diagnosed with HIV at the age of 20 years if started promptly on ART is expected to live a normal life span, with a highly preserved quality of life.(1)	1	1. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One. 2013; 8(12):e81355.
		QoL: Stigma can negatively shape quality of life, affect mental health, and influence ART use and outcomes. **QoL:** Mental health disorders such as these can result in a poorer quality of life and negatively affect access to and use of HIV services."	5	No linked reference
		QoL: Impact of actions taken to reduce stigma & discrimination & address mental health from a quality-of-life perspective (eg, interventions and programs) on these issues as well as on HIV-related health outcomes.	18	No linked reference
7	Ralph et al (2010)	**Mortality/QoL:** no statements linked to references		
8	Strang et al (2016)	**Mortality/QoL:** no statements linked to references		
9	T'Sjoen et al (2020)	**QoL:** Although the quality of sexual life improves after GAMI, research has demonstrated that it does not reach the levels of cisgender people.(44)	575	44. Nobili A, Glazebrook C, Arcelus J. Quality of life of treatment seeking transgender adults: a systematic review and metaanalysis. Rev Endocr Metab Disord 2018;19:199-220.
		QoL: Overall results lean toward favorable sexual outcomes after genital surgeries in trans people, although research into the quality of sexual life in the trans population after GAMI is limited.(44)	580	44. Nobili A, Glazebrook C, Arcelus J. Quality of life of treatment seeking transgender adults: a systematic review and metaanalysis. Rev Endocr Metab Disord 2018;19:199-220.
10	WHO (2011)	**Mortality**: A systematic literature search was conducted on the role of HTC in reducing HIV-related morbidity and mortality, compared with the provision of basic information on HIV prevention and care. The surrogate outcomes were behavioural change and HIV incidence.	39	No direct reference, appears to relate to the systematic review

		Mortality: Alcohol and substance use/dependence is a problem for many MSM and transgender people, and is linked to significant morbidity and mortality.(52)	53	52. Stall R et al. Alcohol use, drug use and alcohol-related problems among men who have sex with men: the Urban Men's Health Study. Addiction, 2001, 96:1589–1601.
		Mortality: OST has been demonstrated to improve both access and adherence to ART, and reduce mortality.(120)	54	120. WHO, UNODC, UNAIDS. *Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users, including access to needle syringe programmes*. Geneva, WHO, 2009. http:// www.unodc.org/documents/hiv-aids/idu_target_setting_guide.pdf (accessed 13 April 2011).
		Mortality: Antiretroviral therapy (ART) is the core pharmacological component of a broad and comprehensive management of HIV infection. ART has significantly decreased the morbidity and mortality from HIV in the past decades. Given that ART represents a biologically targeted intervention, where sexual identities play a minimal role or no role at all on expected effects, there is no reason, biological or other, to differentiate ART recommendations for MSM and transgender people from those formulated for other populations (excluding HIV-infected pregnant women and newborns).	57	No direct reference, appears to come from the systematic review
		QoL: There was no evidence available on issues of quality of life such as inconvenience or decreased desire; however, the values and preferences of the MSM polled by MSMGF showed support for this intervention.(66)	33	66 Arreola S et al. *In our own words: preferences, values, and perspectives on HIV prevention and treatment – a civil society consultation with men who have sex with men and transgender people*. Oakland, California, The Global Forum on MSM and HIV (MSMGF), 2010. http://msmgf.org/files/msmgf//About_Us/Publications/WHO_Report 1.pdf (accessed 19 May 2011)
		QoL: No considerations regarding quality of life such as inconvenience or decreased sexual desire were studied.	35	No direct reference, appears to come from the systematic review
		QoL: No studies were found with information on issues related to quality of life due to the intervention.	44	No direct reference, appears to come from the systematic review
		QoL: Quality of life (inconvenience, unnecessary intervention, anxiety and discrimination) was not measured.	44	No direct reference, appears to come from the systematic review
		QoL: None of the studies reported on HIV or STI incidence or quality of life.	46	No direct reference, appears to come from the systematic review
		QoL: People living with HIV, regardless of ART indication, should also benefit from basic HIV prevention and care, including effective interventions that are simple, relatively inexpensive, improve the quality of life, prevent further transmission of HIV or common opportunistic infections, delay progression of HIV disease and prevent mortality.	59	No linked reference
11	WHO (2012)	**QoL (as QALY):** Using sexual risk behaviour data from the Partners in Prevention trial *(16)*, the cost per HIV infection averted was between US$6000 and $66 000 when PrEP was always used, and the savings per quality-adjusted life year (QALY), a standard measure of cost-benefit, was $260 to $4900. Using "more typical" data that assume less risky sexual behaviour, the cost per HIV infection averted was between ~$0 (break-even) and $26 000 when PrEP was always used, and the cost per QALY gained was between minus $200 (cost-	7	16. Celum C et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. New England Journal of Medicine, 2010, 362(5):427–439.

		saving) and $1900.		
		QoL (as QALY): One cost-effectiveness study in Australia estimated that, if continuous use of PrEP was 90% effective and the program covered only HIV-negative MSM having high-risk sex, it would cost US$47 745 per QALY gained *(18)*. Another cost-effectiveness study from the USA estimated that if PrEP was 90% effective and the program covered only HIV-negative MSM having high-risk sex, it would cost US$107 000 per QALY gained *(19)*. If PrEP was 50% effective, it would cost US$298 000 per QALY gained. Sensitivity analyses showed that the cheaper and more efficacious PrEP is and the more high-risk the population is, the more cost-effective that PrEP would be, with estimates in cost-saving ranging up to over US$300 000 per QALY gained *(20)*. Overall, cost-effectiveness estimates vary widely, depending on model parameter estimates, including efficacy, cost of PrEP, HIV incidence and age of the population.	10-11	18. Anderson J, Cooper D. Cost-effectiveness of pre-exposure prophylaxis for HIV in an MSM population. HIV Medicine, 2009, 10:39. 19. Desai K et al. Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness. AIDS, 2008, 22(14):1829–1839. 20. Paltiel AD et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. Clinical Infectious Diseases, 2009, 48(6):806–815.
12	WHO (2016)	**Mortality:** Access and adherence to OST can improve health outcomes (4), reduce overdose and resulting mortality (54)	33	4. Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, World Health Organization, 2013 and Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, WHO, 2015 (http://www.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf, accessed 25 February 2014). and Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, WHO, 2015. http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf?ua=154. Spire B, Lucas GM, Carrieri MP. Adherence to HIV treatment among IDUs and the role of opioid substitution treatment (OST). International Journal of Drug Policy, 2007, 18(4):262–270 (https://www.plhivpreventionresources.org/index.cfm?action=main.abstract&id=1460 accessed 28 February 2014).
		Mortality: Provision of OST before release can help reduce overdose-related mortality (61).	35	61. Degenhardt L et al. What has been achieved in HIV prevention, treatment and care for people who inject drugs, 2010-2012? A review of the six highest burden countries. International Journal of Drug Policy, 2014, 25:53–60 (http://www.sciencedirect.com/science/article/pii/S095539591300128X, accessed 27 February 2014).
		Mortality: Completing TB treatment is critical to reducing mortality and avoiding the development and spread of drug-resistant TB. It is vital to provide a supportive, non-judgemental and non-discriminatory environment that enables people from key populations to complete treatment, provides additional adherence support measures to improve treatment outcomes, and reduces the risk of continued TB transmission (65). Timely initiation of ART significantly reduces the risk of mortality from HIV-associated TB.	64	65. Policy guidelines for collaborative TB and HIV services for injecting and other drug users: an integrated approach. Geneva, World Health Organization, 2008 (Evidence for Action Technical Papers) (http://whqlibdoc.who.int/publications/2008/9789241596930_eng.pdf accessed 25 February 2014). Integrating collaborative TB and HIV services within a comprehensive package of care for people

				who inject drugs.- Consolidated guidelines. Geneva, WHO, 2016. http://www.who.int/tb/publications/integrating-collaborative-tb-and-hiv_services_for_pwid/en/
		Mortality: Among those living with HIV who are coinfected with HBV or HCV, liver disease progresses more rapidly and mortality is greater than among those with HBV or HCV who are not living with HIV.	67	No linked reference
		Mortality: Coinfection with HIV and HCV accelerates HCV-related progression of liver fibrosis and leads to a higher rate of end-stage liver disease and mortality (121, 151, 157).	68	121. Benhamou Y et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. Hepatology, 1999, 30:1054–1058. 151. Deng LP et al. Impact of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. World Journal of Gastroenterology, 2009, 15:996–1003. 157. Pineda JA et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. Hepatology, 2005, 41:779–789.
		Mortality: These effects may be magnified in low-income and food-insecure contexts, such as those experienced by many key populations. In turn, poor nutritional status can hasten the progression of HIV disease; low body mass index (BMI) in adults (BMI less than 18.5 kg/m2) is an independent risk factor for HIV disease progression and mortality (4).	73	4. Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, World Health Organization, 2013 and Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, WHO, 2015 (http://www.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf, accessed 25 February 2014). and Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, WHO, 2015. http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf?ua=1

Key: ART, antiretroviral therapy; GAMI, gender affirming medical intervention; HIV, human immunodeficiency virus; HTC, HIV testing and counselling; MSM, men who have sex with men; OST,opiate substitution therapy; PrEP, pre-exposure prophylaxis; QALY, Quality-Adjusted Life Year; TB, tuberculosis; * Reference appears in reference list, but not in the main text; ** We believe there is an error here and that the morbidity statement refers to ref 262 not 263. Also noted that references 260 and 261 were the wrong way around.

W5. Extracted Key Recommendations from Clinical Pratice Guidelines

Author (year)	Recommendations
Coleman et al. (2012)	None. Reviewer team were unable to extract key recommendations
Davies et al. (2015)	*Voice and Communication Intervention for Gender Nonconforming Individuals* 1.Transgender voice and communication services should be offered in the context of a complete approach to transgender health that includes comprehensive primary care and a coordinated approach to psychological and social issues. 2.In working with gender nonconforming clients, the speech-language therapist's primary goal is to help the client develop voice and communication that more closely approximates the client's sense of self. 3.Feminizing/masculinizing voice involves nonhabitual use of the voice-producing mechanism. To prevent the possibility of vocal damage, professional evaluation and assistance are essential. 4.Self-guided voice and communication change without professional supervision is not recommended. Clients intending to pursue self-guided voice change should be encouraged to, at a minimum, have an initial professional assessment and then to consult with their primary care provider if they develop symptoms of vocal fatigue or negative changes to vocal quality. Self-help voice and communication groups should have appropriate clinical support. *Clinical Competence* 1.Voice and communication professionals working with transgender individuals must have a basic understanding of transgender health (including hormonal and surgical feminization/masculinization) and trans-specific psychosocial issues; they must be familiar with basic sensitivity protocols such as use of preferred gender pronoun and name. 2.Gender nonconforming individuals who are seeking voice and communication services for reasons other than speech feminization/masculinization can be treated by trans-sensitive speech-language therapists using standard voice and communication protocols. voice and communication feminization/masculinization requires additional clinical expertise and special clinical protocols. *Client Inclusion and Exclusion* 1.Voice and communication services should be available to the full spectrum of the transgender community, including MtF and MtF transsexuals and others who are gender nonconforming. 2.The need for voice and communication services should not be evaluated based on hormonal use, pursuit of sex reassignment surgery, or length or percentage of time living in the desired gender role. 3.Services should be adapted as needed to fit a client's individual needs, including accommodation relating to speech or hearing disability, mental illness, cognitive disability, learning disability, physical disability, geographic isolation, or incarceration. *Treatment Decisions* 1.The client is responsible for treatment decisions, supported by the clinician's informed professional opinion, assessment data, and any allies the client wishes to be involved. To support fully informed treatment decisions, clients should be informed of the following: a.potential risks and benefits associated with treatment options b. estimated duration of treatment; factors that can influence the duration of treatment 2. Existing protocols for voice and communication feminization should be reviewed and considered when developing individualized treatment plans. As there are no established protocols for speech masculinization, FtMs seeking this service should be informed that the protocol is a trial. 3. While modification of existing protocols is encouraged, all treatment plans (including those using new or experimental techniques) are expected to be based on a clearly articulated, logical, and valid clinical rationale. Departure from existing protocols should be explained as such to the client as part of fully informed consent and should be documented in detail to facilitate evaluation. *Assessment* 1.Assessment prior to voice and communication feminization/masculinization should include the following:

		a. psychosocial, voice use, voice health, and medical history b. clinical assessment of speech and voice including: 1.the client's subjective assessment 2.instrumental measurement 3.the clinician's subjective analysis 4.an assessment of potential for change 5.assistance with understanding therapeutic options 2.As there is evidence that behavioral changes (of pitch, inflection, resonance, etc.) may degrade over time, periodic re-evaluation is recommended following treatment with further clinical assistance as needed. *Voice and Communication Therapy* 1.Voice and communication therapy should be individualized based on each person's goals and identity, the risks and benefits of treatment options, and consideration of social and economic issues. 2.Rather than adopting a rigid and artificial set of voice and communication norms, it is recommended that clients be assisted to develop an individualized and context-specific set of norms based on communication patterns in their own social, cultural, work, and home environments. 3.It is clinically optimal to be able to offer both individual sessions and group treatment, with the proportion of time in each format depending on the client's therapeutic needs and goals. *Pitch-Elevating Surgery* 1.As there is no professional consensus regarding the effectiveness and risk-benefit ratio of pitch-elevating surgery, care should be taken to ensure that clients are fully informed of potential risks, postoperative care requirements, and possible outcomes (including decreased pitch). 2.Assessment by both a laryngologist and speech-language therapist is recommended prior to surgery. 3.Prior to surgery, the laryngologist should discuss after-care instructions with the patient and provide written after-care instructions. 4.Voice therapy should be offered following phonosurgery to help the patient adapt to and stabilize the new voice. *Outcome Evaluation* 1.Outcomes should be rigorously evaluated and documented. 2.At minimum, the baseline assessment should be repeated immediately following the end of therapy. Ideally, re-evaluation would take place at 6 months, 1 year, 5 years, and 10 years after treatment. 3.Evaluation should include client satisfaction with the treatment outcome and with the quality of care provided, as well as perceptual and objective measures of voice and communication change. 4.Informal or formal sharing of outcome data (with colleagues, at conferences, in publications, etc.) must occur only if the client has provided fully informed and voluntary written consent. *Research* 1.There is a paucity of data relating to speech feminization/masculinization. Further research in this area is eagerly anticipated. 2.To ensure that participation in research is voluntary, services should not be offered solely as part of a research protocol.
	ECDC (2018)	The ECDC guidance advocates for the development of an integrated national testing strategy or programme for HIV, HBV and HCV. Such integrated testing strategies or programmes should apply the six core testing principles, respect the individual needs of those tested and incorporate evidence-based interventions. Success in increasing the testing uptake should contribute considerably to the elimination of HIV and combat viral hepatitis as public health threat by 2030. *There are six overarching principles for HIV, HBV and HCV testing programmes in this context:* · An effective national testing strategy, including a monitoring and evaluation framework, is critical in responding to HIV, HBV and HCV infection. · Testing should be accessible, voluntary, confidential and contingent on informed consent. · Appropriate information should be available before and after testing. · Linkage to care is a critical part of an effective testing programme. · Normalising HIV, HBV and HCV testing in all healthcare settings; and · Those carrying out HIV, HBV and/or HCV testing should receive appropriate training and education. *Who to test?* The guidance identifies the following population groups suitable for targeted HIV, HBV and HCV testing due to higher risk of infection and suggest to offer tests to: · men who have sex with men (MSM) · trans* people · people who inject drugs (PWID) · migrants2 · household contacts of people diagnosed with HBV · homeless people · sex workers · people in prison · pregnant women · haemodialysis patients · people who have received blood products, organs or surgical interventions before adequate safety and quality regulations were enforced;

		and · sexual or injecting partners of people diagnosed with HIV, HBV and HCV. *Normalising testing* Making the testing offer a routine and with that making the process similar to those for other diagnostic test, helps to reduce stigma and increases testing uptake. The implementation of indicator condition-guided HIV testing provides a useful complement to targeted HIV testing of groups at higher risk. By providing a clinical rationale for testing, this strategy can also help normalise testing and reduce barriers to it, including issues around stigma among healthcare providers and patients alike. *Where to test?* The ECDC guidance outlines where, how and when to test for viral hepatitis and HIV by providing evidence-based options of testing strategies that are applicable to all healthcare settings, as well as testing strategies specifically for: · primary healthcare settings · hospital settings · other healthcare settings (e.g. STI clinics, pharmacies, prisons and some drug and harm reduction services) · community settings (including drug and harm reduction services); and · self-sampling and self-testing. *Frequency of testing* The suggested frequency of testing is3: · For those at risk of HIV infection – at least once a year and up to every three months depending on ongoing risk, sexual behaviour, history of sexually transmitted infections, use of pre- or post-exposure prophylaxis (PrEP, PEP) and local HIV prevalence or incidence. · For those at risk of HBV infection – test those at risk who have not had a complete course of HBV vaccinations based on vaccination history. Retesting up to every 6 to 12 months is only suggested if there is an ongoing risk for either unvaccinated people or vaccine non-responders. · For those at risk of HCV infection – consider testing all sex workers, people who inject drugs, trans* people, prisoners and migrants, and other populations at risk every 6 to 12 months depending on risk profile. *Testing strategies for all settings* *Focus* *I*n areas of intermediate (HBV/HCV) or high prevalence (HBV/HCV/HIV)[4]: · Consider identifying those who are unaware they are infected through geographically targeted routine testing. · Consider birth cohort or universal one-time testing as option to increase HCV testing coverage, taking into account local epidemiology, affordability and the availability of effective linkage-to-care pathways. *In addition*: · Test all patients diagnosed with either HIV, HBV and HCV infection for the other two viruses as per guidelines from the European AIDS Clinical Society (EACS)5 and European Association for the Study of the Liver (EASL)6,7. · As per the ECDC antenatal screening guidance8: offer pregnant women HBV and HIV tests during the first two trimesters of pregnancy. Offer an HCV test depending on the pregnant woman's risk profile. · Only for women at-risk: repeat HIV testing during pregnancy and HBV testing for those who decline HBV vaccination or are non-responders. · When a woman tests negative for HIV or HCV and has a partner at higher risk, facilitate testing of her partner. If the partner remains untested or risk factors are unknown, consider retesting the mother later in pregnancy. · Voluntary partner notification following a positive diagnosis helps to achieve earlier diagnosis and treatment of exposed (sexual) partners. *Testing in primary healthcare settings* Evidence shows that HIV, HBV and HCV testing in primary care (PHC) is acceptable and may effectively contribute to increase testing coverage and case detection. *Focus* Offer integrated testing to any person attending primary care if they: · identify as members of certain risk groups · present with clinical symptoms suggestive of one of three infections; or · show laboratory markers (including elevated liver enzymes) compatible with acute or chronic hepatitis or an HIV indicator condition, including a sexually transmitted infection. Rapid testing, dried blood spot testing and testing using venepuncture are all acceptable in primary care. · Consider offering all patients who were diagnosed with HBV, HCV or HIV a test for the other two viruses. *Considerations* · Although limited, evidence on general population testing in these settings is also encouraging, at least in intermediate- and high-prevalence regions and birth cohorts. · Available evidence suggests testing coverage in primary care settings is often suboptimal and caused by factors that discourage healthcare professionals from offering tests. Consider interventions to increase test offers, including educational interventions for healthcare staff and clinical decision-making tools. · For testing in PHC settings, appropriate clinical care pathways and referral systems need to be established to ensure better linkage to care for people newly diagnosed with HBV, HCV or HIV in primary care. *Testing in hospital settings* Testing for HIV, HBV and HCV in hospital settings is generally accepted by patients and staff and can contribute to better testing coverage and case detection among risk groups or people presenting with HIV indicator conditions. *Focus* Offer integrated testing to any person attending a hospital if they: · identify as members of certain risk groups · present with clinical symptoms suggestive of one of three infections; or · show laboratory markers (including elevated liver enzymes) compatible with acute or chronic hepatitis or an HIV indicator condition, including a sexually transmitted infection. Studies

		indicate that routine testing in emergency departments, including universal testing and integrated testing, is also acceptable to patients and staff in hospitals even though it is currently supported by limited evidence on its effectiveness. *Considerations* · Test all patients diagnosed with an HIV, HBV and HCV infection in hospital settings for the other two viruses, despite little current evidence on effectiveness. · Even though there is little evidence of the effectiveness of any specific intervention over any other, education and training programmes for healthcare staff, campaigns and clinical decision-making tools can support the offer and uptake of integrated testing strategies. *Testing in other healthcare settings* These settings include formal healthcare services (outside hospitals and primary care practices) such as STI, genito-urinary medicine, dermato-venereology and low-threshold clinics, pharmacies, antenatal, prison health, drug and harm reduction and tuberculosis services. *Focus* Based on available evidence for integrated testing in these specific settings: · Consider offering all patients diagnosed with an HBV, HCV or HIV infection a test for the other two viruses. · Ensure that people who are newly diagnosed with HBV, HCV or HIV are linked to care given that efficient testing strategies in these surroundings need appropriate pathways to care and effective referral systems. *Considerations* · Testing for HIV, HBV and HCV, including integrated testing, in such healthcare settings results in varying degrees of effectiveness regarding the increase of testing coverage and case detection. Limited evidence suggests that rapid diagnostic tests and dried blood spot tests are acceptable and may help to increase testing coverage in such sites. · Pharmacies generally offer HIV, HBV and HCV testing under the same quality standards that apply to healthcare settings despite very limited evidence currently on the effectiveness of this activity. · Harm reduction services offer and suggest HBV and HCV testing to everyone attending drug and harm reduction services and during their initial assessments. Repeat this offer in case of indicated ongoing risk. · Sites serving migrant populations can look into offering relevant testing to people who come from countries with intermediate (HCV) or high HIV, HBV and HCV prevalence. · Prison settings can look into offering HIV, HBV and HCV testing to all people in prison as per ECDC guidance on active case finding in prison settings given the higher prevalence of blood-borne viruses in many prison settings. See also the ECDC/European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) guidance on prevention and control of blood-borne viruses in prison settings9. STI/genito-urinary/dermato-venereology clinics can consider offering HIV testing to anyone seeking care regardless of symptoms or risk factors as part of the initial screening for STIs according to the International Union against Sexually Transmitted Infections' European guidelines. This includes offering HIV testing to those who: - have a high likelihood of exposure to HIV - are pregnant regardless of risk factors; or - voluntarily seek testing, especially if never tested before. Based on geographic prevalence and risk group, it may be appropriate to suggest HBV testing. *Testing in community settings* Community-based testing services refers to programmes and services that offer voluntary HIV and/or HBV, HCV testing outside formal healthcare facilities. They are designed to target specific population groups and clearly adapted and accessible to those communities. *Focus* There is a role for community-based testing to target groups at higher risk in any national testing strategy. They are acceptable and effective in increasing HIV, HBV and HCV testing coverage and case detection among these groups. Integrated testing and rapid testing may be offered for everyone accessing drug and harm reduction services in a community or outreach testing activities. Rapid testing in the community is acceptable and contributes to increased testing coverage when implemented in such settings. Options based on available evidence for integrated testing in these settings: · Linkage to care after HBV and HCV testing in community settings may currently be suboptimal, at least for certain risk groups. If testing in community settings is considered within a national testing scheme, clear pathways into care and other services have to be developed. This includes differentiated care pathways for the three infections and other services. · Testing services offered by lay providers help to increase testing opportunities, uptake and coverage. *Self-sampling and self-testing* Self-sampling and self-testing are additional options that give people the flexibility and privacy of performing an initial HIV, HBV and HCV test in their own homes or a place they consider convenient. To date, there is little scientific evidence on the effectiveness of self-sampling, especially relating to HCV and HBV, to reach any firm conclusions regarding inclusion in a national testing strategy. There is limited evidence that kits distributed to people attending an STI clinic may increase test coverage and frequency. *Focus* Self-sampling for HIV, HBV and HCV, including possible integrated sampling, is likely acceptable among those most at-risk and may contribute to increased testing coverage and case detection. Limited available evidence suggests that self-testing for HIV among men who have sex with men is acceptable and may increase testing coverage, frequency and case detection. Self-sampling kits can be effectively distributed through a variety of channels, such as pharmacies, healthcare settings, outreach activities and online platforms, but should be based on local circumstances and target populations *Considerations* To ensure effective linkage to care after self-sampling and/or self-testing as part of a testing strategy, clear pathways to care and other services need to be in place or

		developed, including differentiated care pathways for the three infections. *Contact tracing (includes voluntary partner notification)* Contact tracing, including partner notification, implies that people who may potentially have been exposed to an infection are informed of this possibility and are offered a test. This can also include other interventions depending on the specific infection. Partner notification is a voluntary process in which a trained provider asks a person diagnosed with HIV, HBV and HCV about details of their sexual partners, at-risk drug injecting partners and household contacts as indicated by the diagnosis and then offers to invite them for a test. The identity of the diagnosed person remains anonymous to the contact unless consent is given. *Focus* Even though there is currently limited evidence on the effectiveness of partner notification in increasing testing coverage and case detection, mainly related to HIV, it follows public health logic in response to other communicable diseases to offer voluntary anonymous partner notification to every patient with a newly confirmed diagnosis. There are various strategies to implement partner notification, including passive notification, assisted anonymous notification using a web-based platform and assisted notification with the direct involvement of the service provider. *Considerations* Current implementation of partner notification processes appears to be suboptimal across Europe. While the success of interventions to increase the coverage of partner notification may depend on local factors, including organisational and legal circumstances, educational interventions targeting healthcare workers may prove to be beneficial. *Monitoring integrated national testing strategies or programmes for HBV, HCV and HIV* Monitoring and evaluation is an essential component of any effective testing programme. While strategic information should guide the design of testing initiatives, monitoring and evaluation data permit continuous reevaluation of targets as well as assessment of programme effectiveness, efficiency and impact. Such data can prove invaluable in planning improvements
	Gilligan et al. (2017)	1. Core communication skills 1.1. Before each conversation, clinicians should review the patient's medical information, establish goals for the conversation, and anticipate the needs and responses of the patient and family. 1.2. At the beginning of conversations with patients, clinicians should explore the patient's understanding of their disease and collaboratively set an agenda with the patient after inquiring what the patient and family wish to address and explaining what the clinician wishes to address. 1.3. During patient visits, clinicians should engage in behaviors that actively foster trust, confidence in the clinician, and collaboration. 1.4. Clinicians should provide information that is timely and oriented to the patient's concerns and preferences for information. After providing information, clinicians should check for patient understanding and document important discussions in the medical record. 1.5. When patients display emotion through verbal or nonverbal behavior, clinicians should respond empathically. 2. Discussing goals of care and prognosis 2.1. Clinicians should provide diagnostic and prognostic information that is tailored to the patient's needs and that provides hope and reassurance without misleading the patient. 2.2. Clinicians should reassess a patient's goals, priorities, and desire for information whenever a significant change in the patient's care is being considered. 2.3. Clinicians should provide information in simple and direct terms. 2.4. When providing bad news, clinicians should take additional steps to address the needs and responses of patients. 3. Discussing treatment options and clinical trials 3.1. Before discussing specific treatment options with the patient, clinicians should clarify the goals of treatment (cure v prolongation of survival v improved quality of life) so that the patient understands likely outcomes and can relate the goals of treatment to their goals of care. 3.2. When reviewing treatment options with patients, clinicians should provide information about the potential benefits and burdens of any treatment (proportionality) and check the patient's understanding of these benefits and burdens. 3.3. Clinicians should discuss treatment options in a way that preserves patient hope, promotes autonomy, and facilitates understanding. 3.4. Clinicians should make patients aware of all treatment options, including clinical trials and a sole focus on palliative care. When appropriate, clinicians should discuss the option of initiating palliative care simultaneously with other treatment modalities. If clinical trials are available, clinicians should start treatment discussions with standard treatments available off trial and then move to a discussion of applicable clinical trials if the patient is interested. 4. Discussing end-of-life care 4.1. Clinicians should use an organized framework to guide the bidirectional communication about end-of-life care with patients and families. 4.2. Clinicians should initiate conversations about patients' end-of-life preferences early in the course of incurable illness and readdress this topic periodically based on clinical events or

		patient preferences. 4.3. Clinicians should explore how a patient's culture, religion, or spiritual belief system affects their end-of-life decision making or care preferences. 4.4. Clinicians should recognize and respond empathically to grief and loss among patients, families, and themselves. Clinicians should refer patients and families to psychosocial team members (eg, social workers, counselors, psychologists, psychiatrists, and clergy) when appropriate. 4.5. Clinicians should identify and suggest local resources to provide robust support to patients, families, and loved ones transitioning to end-of-life care. 5. Using communication to facilitate family involvement in care 5.1. Clinicians should suggest family and/or caregiver involvement in discussions (with patient consent) early in the course of the illness for support and discussion about goals of care. 5.2. Determine if a formal family meeting in a hospital or outpatient setting is indicated at important junctures in care. When possible, ensure that patients, their designated surrogates, and desired medical professionals are present. 6. Communicating effectively when there are barriers to communication 6.1. For families who do not share a common language with the clinician, use a medical interpreter rather than a family interpreter. 6.2. For patients with low health literacy, focus on the most important points, use plain language, and check frequently for understanding. 6.3. For patients with low health numeracy, use pictographs or other visual aids when available, and describe absolute risk rather than relative risk. 7. Discussing cost of care 7. Clinicians should explore whether cost of care is a concern for patients with cancer. 8. Meeting the needs of underserved populations 8.1. Enter clinical encounters with a sense of curiosity, aware that any patient and family, regardless of their background, may have beliefs, experiences, understandings, and expectations that are different from the clinician's. 8.2. Avoid assumptions about sexual orientation and gender identity and use nonjudgmental language when discussing sexuality and sexual behavior. 8.3. Remain aware that members of underserved or marginalized populations have an increased likelihood of having had negative past health care experiences, including feeling disrespected, alienated, or unsafe. 9. Clinician training in communication skills 9.1. Communication skills training should be based on sound educational principles and include and emphasize skills practice and experiential learning using role-play scenarios, direct observation of patient encounters, and other validated techniques. 9.2. For communication skills training to be most effective, it should foster practitioner self-awareness and situational awareness related to emotions, attitudes, and underlying beliefs that may affect communication as well as awareness of implicit biases that may affect decision making. 9.3. Facilitators of communication skills training should have sufficient training and experience to effectively model and teach the desired communication skills and facilitate experiential learning exercises.
5	Hembree et al. (2017)	*1.0 Evaluation of youth and adults* 1.1. We advise that only trained mental health professionals (MHPs) {and/or trained physicians**}** who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. 1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. 1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. 1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence.

		1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. *2.0 Treatment of adolescents* 2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. 2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty. 2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. 2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years. 2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. 2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment. *3.0 Hormonal therapy for transgender adults* 3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. 3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. 3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. 3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. *4.0 Adverse outcome prevention and long-term care* 4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. 4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. 4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. 4.4. We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. 4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females. 4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. 4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. *5.0 Surgery for sex reassignment and gender confirmation* 5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. 5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. 5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. 5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes.

		5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. 5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement.
	IAPHCCO (2015)	*Optimizing the HIV care environment* 1. Laws that criminalize the conduct of or exert punitive legal measures against MSM, transgender individuals, substance users, and sex workers are not recommended and should be repealed where they have been enacted. 2. Laws that criminalize the conduct of PLHIV based on perceived exposure to HIV, and without any evidence of intent to do harm, are not recommended and should be repealed where they have been enacted. 3. HIV-related restrictions on entry, stay, and residence in any country for PLHIV are not recommended and should be repealed where they have been enacted. 4. Strategies to monitor for and eliminate stigma and discrimination based on race, ethnicity, gender, age, sexual orientation, and/or behavior in all settings, but particularly in health care settings, using standardized measures and evidence-based approaches, are recommended. 5. Proactive steps are recommended to identify and manage clinical mental health disorders (eg, anxiety, depression, and traumatic stress) and/or mental health issues related to HIV diagnosis, disclosure of HIV status, and/or HIV treatment. 6. Enabling PLHIV to take responsibility for their care (eg, self-management, user-driven care) is recommended. 7. Shifting and sharing HIV testing, dispensing of ART, and other appropriate tasks among professional and paraprofessional health worker cadres is recommended. 7a. Use of lay health workers to provide pretest education and testing and to enhance PLHIV engagement in HIV care is recommended. 7b. Task shifting/sharing from physicians to appropriately trained health care providers, including nurses and associate clinicians, is recommended for ART initiation and maintenance. 8. Community engagement in every step across the HIV care continuum is recommended. *Increasing HIV testing coverage and linkage to care* 9. Routinely offering opt-out HIV testing to all individuals who present at health facilities is recommended. 10. Community-based HIV testing is recommended to reach those who are less likely to attend facility-based HIV testing. 11. Confidential, voluntary HIV testing in large workplace and institutional settings (military, police, mining/trucking companies, and educational venues) should be considered. (B III) 12. HIV self-testing is recommended with the provision of guidance about the proper method for administering the test and direction on what to do once the results have been obtained. 13. Use of epidemiological data and network analyses to identify individuals at risk of HIV infection for HIV testing is recommended. 14. The offer of HIV testing to partners of newly diagnosed individuals is recommended. 15. Immediate referral to HIV care is recommended following an HIV-positive diagnosis to improve linkage to ART. 16. For high-risk individuals who test HIV negative, offering PrEP is recommended in addition to the provision of free condoms, education about risk reduction strategies, PEP, and voluntary medical male circumcision. 17. Use of case managers and patient navigators to increase linkage to care is recommended. *Increasing HIV treatment coverage* 18. The immediate offer of ART after HIV diagnosis, irrespective of CD4 count or clinical stage, is recommended. 19. First-line ARV regimens with the highest levels of efficacy, lowest adverse event profiles, and delivered in QD fixed-dose combinations are recommended. 20. Viral load testing at least every 6 months is recommended as the preferred tool for monitoring ART response. 21. HIV drug resistance testing is recommended at entry into care or prior to ART initiation and when virologic failure is confirmed. 21a. Where routine access to HIV drug resistance testing is restricted, population-based surveillance is recommended. 22. Community-located ART distribution is recommended. 22a. The use of community-based pharmacies should be considered. *Increasing retention in care, ART adherence, and viral suppression* 23. Systematic monitoring of retention in HIV care is recommended for all patients. 23a. Retention in HIV care should be considered as a quality indicator. 23b. Measuring retention in HIV care using electronic health record and other health system data is recommended. 23c. Use of clinic databases/surveillance systems for HIV clinical monitoring and population-level tracking is recommended.

		24. Routine ART adherence monitoring is recommended in all patients. 24a. Viral suppression is recommended as the primary adherence monitoring metric. 24b. Routine collection of self-reported adherence data from patients is recommended. 24c. Pharmacy refill data are recommended for adherence monitoring. 25. Information and communication technologies aimed at supporting patient self-care are recommended. 25a. Mobile health technology using weekly interactive components (eg, 2-way SMS) is recommended. 25b. Alarm devices are recommended as reminders for PLHIV with memory impairment. 26. Patient education about and offering support for medication adherence and keeping clinic appointments are recommended. 26a. Pillbox organizers are recommended, particularly for HIV-infected adults with lifestyle-related barriers to adherence. 27. Neither directly administered nor directly observed ART is recommended for routine clinical care settings. 27a.DirectlyadministeredARTis recommended for people who inject drugs and released prisoners at high risk of ARTnon adherence. 28. Proactive engagement and reengagement of patients who miss clinic appointments and/or are lost to follow-up, including intensive outreach for those not engaged in care within 1 month of a new HIV diagnosis, is recommended. 28a. Case management to retain PLHIV in care and to locate and reengage patients lost to follow-up is recommended. (B II) 28b. Transportation support for PLHIV to attend their clinic visits is recommended. *Adolescents* 29. Removing adult-assisted consent to HIV testing and counseling is recommended for minor adolescents with the capacity to consent. (B II) 30. Adolescent-centered services are recommended in both clinical and community-based settings. 31. Informing an adolescent of his/her HIV-positive diagnosis is recommended as soon after diagnosis as feasible. (B II) 32. A transition plan between pediatric and adult HIV care is recommended. *Metrics for and monitoring of the HIV care continuum* 33. A standardized method should be used to estimate the total number of PLHIV (diagnosed and undiagnosed) within a geographi csetting. 34. The estimated number of PLHIV in the geographic setting should be the overall denominator for the HIV care continuum. 35. Collection of a minimum set of 5 data elements should be considered to populate the HIV care continuum. Estimated number of PLHIV Number and proportion of PLHIV who are diagnosed as having HIV Number and proportion of PLHIV who are linked to care (optional) Number and proportion of PLHIV on ART Number and proportion of PLHIV on ART who are virally suppressed 36. Where possible, jurisdictions should consider longitudinal cohort measurement of HIV service utilization and treatment outcomes to identify the means to maximize viral suppression through ensuring early access to ART and retention in care.
7	Ralph et al. (2010)	*Recommendation for Penile Fracture* Imaging (cavernosography, US, or MRI) can be used for localization of the injury, while retrograde urethrogram (pre-/perioperative) can be performed if there is a suspicion of a urethral injury. The ultimate decision for surgery is based on clinical findings and once diagnosed, there is no indication for conservative management. *Recommendation for Skin Loss Injuries* There is evidence to support surgical replacement of shaft skin with either split, mesh, or full thickness skin. *Recommendation for Penile Amputation* Critical warm and cold ischemia time is unknown. Surgical reattachment is therefore a clinical decision and is best performed by an experienced microsurgeon. Psychological evaluation should be offered to patients who self-mutilate. If re-implantation fails or is impossible, patients should be referred for phalloplasty at an appropriate time interval. *Definition of Gender Identity Disorder/ Transexualism* The desire for at least 2 years, to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone therapy. *Male-to-Female Genital Surgery* Bilateral orchiectomy, amputation of the corpora cavernosa, creation of a neovaginal cavity that is lined by hairless skin, the formation of a sensate neoclitoris, and an aesthetic vulval appearance are the aims of genital surgery. The outcome may be achieved in one or two stages with satisfaction rates of 80% expected. *Female-to-Male Genital Surgery*

		Breast reduction, oophorectomy, hysterectomy, and vaginectomy should be offered to all patients. There are many phalloplasty techniques involving local or free flaps and mircrosurgery. Patients should be warned that multiple stages are often needed with high urethral and prosthetic complication rates. However, a universal satisfaction rate of 80% should be expected. Metoidioplasty can be offered to those who wish to stand to void but do not want sexual intercourse. *Penile Augmentation – Indications* A stretched penile length of <7cm should be considered as a micropenis with many surgical techniques being recommended. The indications for augmentation in men with a normal-sized penis cannot be drawn from the literature *Penile Augmentation – Surgical Techniques* There are many lengthening techniques described with variable success rates. The complications may be significant. Stretching devices may be an alternative treatment option. All operative methods of girth enhancement have no proven efficacy outcome data. Liquid silicone injection should be discouraged. Psychological assessment should proceed any surgical approach
	Strang et al. (2016)	*Emergency intakes:* If the adolescent presents in a state of emergency, as some gender dysphoria (GD) referrals do, then as in any assessment, the first priority is risk reduction/safety. Hospitalization may be necessary in extreme cases to prevent self-harm/mutilation, though psychiatric hospital units are often not equipped to work with gender dysphoric adolescents with autism spectrum disorders (ASD), and so outside consultation to the unit may be necessary. Ultimately, engaging a therapist with training (or consultation support) in both ASD and gender nonconformity/GD may be a critical step; helping a patient understand that relief is coming and that their gender-needs will be addressed may reduce safety risks, and support further assessment. *ASD assessment:* When an ASD diagnosis is suspected, it is important for an autism specialist to confirm the diagnosis, if a diagnosis has not been established. Whenever possible, a neuropsychological/autism evaluation should be conducted to evaluate the impact of ASD on an adolescent's ability to understand and report GD symptoms as well as engage in therapy/treatments. Evaluations should include assessment of general cognitive skills, executive function skills (impulse control, flexibility, planning, future thinking), communication skills, emotional functioning, self-awareness/social cognition, and capacity for self-advocacy. Knowledge of the young person's capacities will inform the GD diagnosis process (i.e., how to best obtain clinical/diagnostic information and understand that information), as well as deciding on clinical treatment options (i.e., the ability to understand treatments, comply with treatments, consider a range of gender possibilities vs. concrete/black-and-white thinking). *Gender-related assessment:* When gender issues are reported/suspected in an adolescent with ASD, a structured interview should be used to assess for gender dysphoria, including dysphoria over time, intensity of dysphoria, and its pervasiveness. Whenever possible, it is important to obtain additional report from other sources (e.g., parents), as communication, self-awareness, and self-advocacy skills may be vulnerable in adolescents with ASD. It is difficult to separate the assessment and treatment of many of these individuals, because assessment continues throughout the treatment process as the person may develop increased understanding of themselves and increased ability to express their wants and needs. Therefore, gender-related diagnostics may take more time. For some individuals, however, GD diagnosis is immediately clear, such as when the dysphoria has been present for an extended period, the young person is already presenting as a different gender, or when the level of urgency about gender transition is extreme. *Treatment checklist (psychosocial and medical).* Establish appropriate clinical team, ideally a clinician trained in both autism spectrum disorders (ASD) and gender nonconformity/ gender dysphoria (GNC/GD), or clinicians collaborating from each specialty. Address and assess intensity of gender feelings/urgency throughout the treatment process, as assessment often continues during treatment, informing and shaping the goals of the treatment. Key clinical questions: a. Is the GD clear, urgent, pervasive, and persistent over time (i.e., meeting full diagnostic criteria for GD)? If yes, consultation with medical transition services may be indicated (see "If medical transition is indicated" below). b. Does the GD increase or decrease with intervention (e.g., as adolescent develops increased social/self-awareness, executive function flexibility and big picture thinking skills, communication/self-advocacy skills)? Provide psycho-education about and explore the possibility of a range of gender outcomes (e.g., gender spectrum, incorporating aspects of a different gender without full gender transition, etc.) This may require specific approaches targeting ASD related deficits in cognitive flexibility (i.e., reducing all or nothing/black and white thinking). Provide structure, as necessary, for gender exploration, supporting the adolescent's ability to explore gender transition, including clothing, name, pronouns, etc. Parents may need to assume a central role in helping facilitate an individual's exploration of their gender when ASD-related weaknesses in daily living skills, planning and self-advocacy interfere with that

		exploration. Such family support may include reminding a young person of their gender exploration therapy goals during the week, helping a young person to obtain appropriate clothing to try on, and so forth. Over the course of treatment, assess for signs that the adolescent's experience of GNC/GD is caused by comorbidities or symptoms of ASD (e.g., ASD preoccupations, misinterpreting sexual orientation for gender, etc.) If it becomes clear that a wish to transition is caused by a comorbidity or symptoms of ASD, explore alternative solutions to gender transition. If medical transition is indicated during the process, ensure that a pediatric endocrinologist (or similar medical specialist) trained in GD is engaged in the treatment to discuss risks/benefits of pubertal blockade and/or cross sex hormones. The endocrinologist/medical specialist and other treatment providers (e.g., autism specialist) should collaborate around diagnostics and treatments. If medical treatments begin, provide concrete psycho-education about treatment side effects, risks and benefits and ensure that these issues are understood by the adolescent with concurrent GD and ASD. Consider the accessibility and appropriateness of adjunct gender and/or ASD-related supports/services. Provide support, coaching, and vetting as needed. For example, an LGBT youth group leader may require some coaching in how to welcome and engage a person with ASD, and an autism skills group provider may require support in how to work with a GD/gender nonconforming adolescent.
	T'Sjoen et al. (2020)	1.We advise that HCPs when working with trans people recognize the diversity of genders, including male, female, and nonbinary individuals. 2. We advise that HCPs when working with trans people openly ask for the individual gender experience of the person seeking treatment, including which pronouns and name they like to be addressed with, and recognize this may change in the future. 3. We advise that HCPs when working with trans people critically reflect upon discriminatory factors influencing both access to and outcomes of gender-related health-care services and make the necessary changes to accommodate all trans individuals. 4. We advise that HCPs when working with trans people should critically reflect on their own possible prejudices, ethics, and power positions. 5. We advise that HCPs when working with adult trans people should explain the result of the clinical assessment with the aim of a shared understanding and shared responsibility. 6. We advise that HCPs assessing gender diverse children and adolescents support the exploration and expression of the youth's experienced gender and help to reduce experienced barriers for those seeking care. 7. We advise that HCPs assessing gender diverse children and adolescents take a developmental approach that includes that gender-related developmental pathways may be more open to change in prepubescent gender diverse children than in pubescent gender diverse adolescents and adults. 8. We advise that HCPs assessing gender diverse children and adolescents assess resilience and vulnerabilities and treat (or refer for treatment) possible mental health problems. 9. We advise that HCPs assessing gender diverse children and adolescents support parents and/or legal guardian and school and other important social networks (when possible) to provide a safe and accepting home and school environment. 10. For prepubescent gender diverse children who desire to live in a role consistent with their experienced gender identity, we advise the HCPs advise that parents and the social environment consider social transitioning of the child after discussing the pros and the cons and while providing continuous psychological support. 11. For pubertal gender diverse adolescents, we advise that HCPs inform and explore all nonmedical and medical options, including the effect that GAMIs (puberty blockers, hormones as well as surgical) may have on sexuality and fertility and if indicated, facilitate GAMIs. 12. In countries requiring an assessment process including a clinical diagnosis to access GAMI, we advise that HCPs assessing trans adolescents for GAMI have the expertise in reaching the required diagnosis for their health service 13. We advise that HCPs working with trans people should inform trans adults seeking GAMI of its effect and assess the capacity of the individual to reach an informed consent regarding GAMI. 14. We advise that, in view of the strong evidence regarding the high levels of mental health problems in adults presenting at trans health services, particularly in those not on hormone treatment, HCPs whose role is informing and assessing the capacity to consent for GAMI in trans people wishing these interventions should have expertise in mental health to be able to identify those requiring further support from mental health professionals to allow for the best possible outcome of GAMI. 15. We advise that HCPs whose role is informing and assessing the capacity to consent for GAMI in trans people wishing these interventions should explore resilience and social support, in view of its association with health-related quality of life and psychological well-being. 16. We advise that HCPs whose role is informing and assessing the capacity to consent for GAMI in trans people wishing these interventions should inform clients about the effect that GAMIs (hormones and surgical) may have on sexual health and fertility. 17. In countries requiring an assessment process including a clinical diagnosis to access GAMI, we advise that HCPs assessing trans adults for GAMI have the expertise in reaching the required diagnosis for their health service. 18. We advise initiating pubertal hormone suppression in trans adolescents, when gender incongruence or nonconformity is assessed, interfering psychosocial difficulties are addressed if possible, and after they show their first pubertal changes (Tanner stage G2) and when they have sufficient capacity to give informed consent.

		19. We advise in adolescents desiring masculinizing hormone treatment, when they have sufficient capacity to give informed consent, puberty induction with testosterone, often using a gradually increasing dose schedule. 20. We advise that before initiation of gonadotropin-releasing hormone analogs (GnRHa) or progestogen and/or testosterone, the hormone-prescribing physician should screen for conditions that may worsen with the start of treatment. 21. If masculinization is desired, we advise testosterone therapy with monitoring of serum sex steroid levels and signs of virilization. 22. We advise the hormone-prescribing physician discusses the effects and possible adverse health effects of GnRHa, progestogen, and/or testosterone treatment, including fertility preservation options, based on the person's goals before any hormonal intervention. 23. We advise informing trans subjects on the expected changes upon GnRHa, progestogen, and/or testosterone initiation on its effect on body satisfaction and on sexual function (desire and activity) and considering the role that factors such as relationship status and possible surgical interventions will play. 24. We advise initiating pubertal hormone suppression in trans adolescents, when gender incongruence or nonconformity is assessed, interfering psychosocial difficulties are addressed if possible, and after they show their first pubertal changes (Tanner stage G2) and when they have sufficient capacity to give informed consent. 25. We advise in adolescents desiring feminizing hormone treatment, when they have sufficient capacity to give informed consent, puberty induction with 17beta-estradiol, often using a gradually increasing dose schedule. 26. We advise that before initiation of GnRHa or antiandrogen and/or estrogen treatment, the hormone-prescribing physician needs to screen for conditions that may worsen with the start of treatment. 27. If feminization is desired, we advise estrogens and/or antiandrogen therapy with monitoring of serum sex steroid levels and signs of feminization. 28. We advise the hormone-prescribing physician discusses the effects and possible adverse health effects of GnRHa, antiandrogen, and/or estrogen treatment, including fertility preservation options and consequences for genital surgery, based on the person's goals before any hormonal intervention. 29. We advise informing trans clients on the expected changes upon GnRHa, estrogen, and/or anti-androgen initiation and its effect on body satisfaction, sexual desire and activity and considering the role factors such as relationship status and possible surgical interventions can play 30. We advise HCPs should be aware of potential sexual problems during all surgical phases of treatment. 31. We advise that regardless of surgical pathways, HCPs should be aware of diversity in sexual practices in trans people. 32. We advise that surgeons performing GAS collaborate with sexologists with knowledge and experience with trans people, if available.
	WHO (2011)	*Recommendations on human rights and non-discrimination in health-care settings* 1. Legislators and other government authorities should establish antidiscrimination and protective laws, derived from international human rights standards, in order to eliminate discrimination and violence faced by MSM and transgender people, and reduce their vulnerability to infection with HIV, and the impacts of HIV and AIDS. 2. Health services should be made inclusive of MSM and transgender people, based on the principles of medical ethics and the right to health. *Recommendations on HIV prevention, care and treatment* *Prevention of sexual transmission* 3. Using condoms consistently during anal intercourse is strongly recommended for MSM and transgender people over not using condoms. 4. Using condoms consistently is strongly recommended over serosorting for HIV-negative MSM and transgender people. Serosorting is suggested over not using condoms by HIV-negative MSM and transgender people under specific circumstances as a harm reduction strategy. 5. Not offering adult male circumcision to MSM and transgender people for the prevention of HIV and STI is suggested over offering it 6. Offering HIV testing and counselling to MSM and transgender people is strongly recommended over not offering this intervention 7. Offering community-based HIV testing and counselling linked to care and treatment to MSM and transgender people is strongly recommended over not offering such programmes *Behavioural interventions, information, education, communication* 8. Implementing individual-level behavioural interventions for the prevention of HIV and STIs among MSM and transgender people is suggested over not implementing such interventions. 9. Implementing community-level behavioural interventions for the prevention of HIV and STIs among MSM and transgender people is suggested over not implementing such interventions. 10. Offering targeted internet-based information to decrease risky sexual behaviours and increase uptake of HIV testing and counselling among MSM and transgender people is suggested over not offering such information. 11. Using social marketing strategies to increase the uptake of HIV/STI testing and counselling and HIV services among MSM and transgender people is suggested over not using such

		strategies. 12. Implementing sex venue-based outreach strategies to decrease risky sexual behaviour and increase uptake of HIV testing and counselling among MSM and transgender people is suggested over not implementing such strategies. Substance use and prevention of bloodborne infections 13. MSM and transgender people with harmful alcohol or other substance use should have access to evidence-based brief psychosocial interventions involving assessment, specific feedback and advice. 14. MSM and transgender people who inject drugs should have access to needle and syringe programmes and opioid substitution therapy. 15. Transgender people who inject substances for gender enhancement should use sterile injecting equipment and practise safe injecting behaviours to reduce the risk of infection with bloodborne pathogens such as HIV, hepatitis B and hepatitis C. *HIV care and treatment* 16. MSM and transgender people living with HIV should have the same access to ART as other populations. ART should be initiated at CD4 counts of ≤350 cells/mm3 (and for those in WHO clinical stage 3 or 4 if CD4 testing is not available). Access should also include management of opportunistic infections, co-morbidities and treatment failure. 17. MSM and transgender people living with HIV should have access to essential interventions to prevent illness and HIV transmission including, but not limited to, care and support and antiretroviral therapy. *Recommendations on prevention and care of other sexually transmitted infections* 18. MSM and transgender people with symptomatic STIs should seek and be offered syndromic management and treatment. 19. Offering periodic testing for asymptomatic urethral and rectal N. gonorrhoeae and C. trachomatis infections using NAAT is suggested over not offering such testing for MSM and transgender people. Not offering periodic testing for asymptomatic urethral and rectal N. gonorrhoeae infections using culture is suggested over offering such testing for MSM and transgender people. 20. Offering periodic serological testing for asymptomatic syphilis infection to MSM and transgender people is strongly recommended over not offering such screening 21. MSM and transgender people should be included in catch-up HBV immunization strategies in settings where infant immunization has not reached full coverage
	WHO (2012)	1: In countries where HIV transmission occurs among serodiscordant couples, where discordant couples can be identified and where additional HIV prevention choices for them are needed, daily oral PrEP (specifically tenofovir or the combination of tenofovir and emtricitabine) may be considered as a possible additional intervention for the uninfected partner. 2: In countries where HIV transmission occurs among men and transgender women who have sex with men and additional HIV prevention choices for them are needed, daily oral PrEP (specifically the combination of tenofovir and emtricitabine) may be considered as a possible additional intervention.
	WHO (2016)	*HIV prevention* 1 The correct and consistent use of condoms with condom-compatible lubricants is recommended for all key populations to prevent sexual transmission of HIV and sexually transmitted infections (STIs). 2 Oral pre-exposure prophylaxis (PrEP) containing tenofovir disproxil fumerate (TDF) should be offered as an additional prevention choice for key populations at substantial risk of HIV infection as part of combination HIV prevention approaches. 3 Post-exposure prophylaxis (PEP) should be available to all eligible people from key populations on a voluntary basis after possible exposure to HIV. 4 Voluntary medical male circumcision (VMMC) is recommended as an additional important strategy for the prevention of heterosexually acquired HIV infection in men, particularly in settings with hyperendemic and generalized HIV epidemics and low prevalence of male circumcision. *Harm reduction* 5 All people from key populations who inject drugs should have access to sterile injecting equipment through needle and syringe programmes. 6 All people from key populations who are dependent on opioids should be offered and have access to opioid substitution therapy in keeping with WHO guidance. 7 All people from key populations with harmful alcohol or other substance use should have access to evidence-based interventions, including brief psychosocial interventions involving assessment, specific feedback and advice. 8 People likely to witness an opioid overdose should have access to naloxone and be instructed in its use for emergency management of suspected opioid overdose. *HIV testing and counselling (HTC)* 9 Voluntary HTC should be routinely offered to all key populations both in the community and in clinical settings. Community-based HIV testing and counselling for key populations, linked to prevention, care and treatment services, is recommended, in addition to provider-initiated testing and counselling. *HIV treatment and care*

		10 Key populations living with HIV should have the same access to antiretroviral therapy (ART) and to ART management as other populations. 11 All pregnant women from key populations should have the same access to services for prevention of mother-to-child transmission of HIV (PMTCT) and follow the same recommendations as women in other populations. *Prevention and management of coinfections and co-morbidities* 12 Key populations should have the same access to tuberculosis prevention, screening and treatment services as other populations at risk of or living with HIV. 13 Key populations should have the same access to hepatitis B and C prevention, screening and treatment services as other populations at risk of or living with HIV. 14 Routine screening and management of mental health disorders (depression and psychosocial stress) should be provided for people from key populations living with HIV in order to optimize health outcomes and improve their adherence to ART. Management can range from co-counselling for HIV and depression to appropriate medical therapies. *Sexual and reproductive health* 15 Screening, diagnosis and treatment of sexually transmitted infections should be offered routinely as part of comprehensive HIV prevention and care for key populations. 16 People from key populations, including those living with HIV, should be able to experience full, pleasurable sex lives and have access to a range of reproductive options. 17 Abortion laws and services should protect the health and human rights of all women, including those from key populations. 18 It is important to offer cervical cancer screening to all women from key populations, as indicated in the WHO 2013 cervical cancer screening guidelines. 19 It is important that all women from key populations have the same support and access to services related to conception and pregnancy care, as indicated by WHO guidelines, as women from other populations. *Critical enablers* 1 Laws, policies and practices should be reviewed and revised where necessary, and countries should work towards decriminalization of behaviours such as drug use/injecting, sex work, same-sex activity and non-conforming gender identity and toward elimination of the unjust application of civil law and regulations against people who use/inject drugs, sex workers, men who have sex with men and transgender people. 2 Countries should work towards implementing and enforcing antidiscrimination and protective laws, derived from human rights standards, to eliminate stigma, discrimination and violence against people from key populations. 3 Health services should be made available, accessible and acceptable to key populations, based on the principles of medical ethics, avoidance of stigma, non-discrimination and the right to health. 4 Programmes should work toward implementing a package of interventions to enhance community empowerment among key populations. 5 Violence against people from key populations should be prevented and addressed in partnership with key population led organizations. All violence against people from key populations should be monitored and reported, and redress mechanisms should be established to provide justice

Key: {text}, appeared in corrected version; AIDS acquired immune deficiency syndrome; ART, antiretroviral therapy; CD4, T-cell; ECDC, European Centre for Disease Prevention and Control; FtM, female to male; GAMI, gender affirming medical intervention; GAS, gender affirming surgery; HBV, hepatitis B virus; HCV, hepatitis C virus; HCP, health care professional; HIV, human immunodeficiency virus, MSM, men who have sex with men; MtF, male to female; PWID people who inject drugs; STI, sexually transmitted infection; WHO, World Health Organization.

Dear Dr Wim Weber and *The BMJ* editorial team,

Please accept this letter and rebuttal table as an appeal against rejection of our submission 'International Clinical Practice Guidelines for Gender Minority/Trans People: Systematic Review and Quality Assessment' (BMJ-2020-061348).

We have substantially revised the manuscript, which we hope you will invite us to resubmit. We are fully aware that this does not guarantee acceptance. The seven excellent peer reviews and your constructive editorial comments made us realize we had done an inadequate job of explaining the scientific rationale, content and implications of our research for clinicians, policy makers and patients. The detailed feedback and interest in the topic expressed by the international expert reviewers allowed us to re-visit and improve all parts of the manuscript, which is now a much better, timelier and potentially impactful paper.

Specifically:

(1) The reviewers' questions and concerns are all comprehensively answered in the following 21-page rebuttal table.
(2) Systematic guideline review is a novel and emergent area (inevitably narrative and descriptive), but we have improved our rationale, the explanation of added innovation, the interpretation and flow from question to consistent conclusions.
(3) We had failed to justify the logic for certain decisions in our study, but have added a stronger research design strategy section to explain the methods.
(4) We had not initially supplied two further supplementary tables in the results section regarding extracted data, which support and explain the interpretation – our holding back of these original research findings and underestimating the degree to which reviewers might be interested in seeing those results, explains some misunderstanding.
(5) We have significantly revised the manuscript to highlight relevant content and improve style. We have rewritten the introduction and discussion, with a more dispassionate tone and fewer references.
(6) We believe the paper is of interest and relevant to generalists in the UK and worldwide. Clinicians around the world are likely to meet gender minority/trans people during their time in practice, and may perhaps rely on the guidelines appraised by our study. Our findings will help doctors make better decisions and consider research priorities.
(7) We now make more obvious that gender minority/ trans populations are entitled to high quality guidelines and their specific needs should be considered as a matter of equity within all general healthcare guidelines.
(8) The subject is more topical than at initial submission following the recent Judicial Review on puberty blockers, a substantial event within the UK for this field of clinical practice, which has dismayed many within the gender minority/trans community.
(9) Our paper goes some way to stay on neutral, scientific ground, offering positive ways forward in a sensitive, political debate.
(10) We hope *The BMJ* will publish, possibly with an accompanying commentary (or even a 'head-to-head' debate).
(11) If accepted, we would plan to work both with stakeholders and the evidence-based medicine community to ensure a balanced and positive reception/ press release.

Thank you for acknowledging this somewhat exceptional circumstance. We appreciate your careful re-consideration.

Yours sincerely,
Sara Dahlen, on behalf of the research team

(This was sent to BMJ editorial office 17.12.20. Page/line numbers of table below revised to correspond with the manuscript reformatted for BMJ Open 15.1.21)

International Clinical Practice Guidelines for Gender Minority/Trans People: Systematic Review

BMJ Editorial Committee	Our response	Pg/ Ln
We thought your study addresses an important and interesting research question. After discussion, however, we felt that it did not add enough to take it further towards publication in The BMJ.	Thank you. We agree. We appreciate the peer reviewers' careful consideration and constructive comments. The manuscript is greatly improved. We are grateful to you for considering an appeal.	
We had the following concerns. The paper is a largely descriptive/narrative evaluation. It might be useful to identify and summarize the quality of guidelines in this area, but we feel the paper is rather opinionated at places.	We agree about the usefulness, but a systematic review (SR) of guidelines can only be descriptive. We realize we had hidden the enlightening findings 'under a bushel'. We have rewritten the paper, revised the introduction, explained the rationale and context better, added 2 supplementary tables with information about the guidelines' content and improved the discussion. We address a contemporary and contested area, and the paper has potential for high impact.	All
The abstract conclusion, for example, does not flow entirely from the findings.	The abstract conclusion now flows from the findings.	**3-4**
Also, it does not seem necessarily wrong for a specialty society to produce very narrow guidelines about, for example, HIV, so the criticism about 'limited guidance' seems unwarranted.	Thank you. We have improved interpretation. The narrower, and better (HIV), guidelines were largely written by WHO, not specialty societies. The problem is not that guidance is written from an HIV or public health pandemic perspective *per se*, but that we found so little general guidance even from the relevant specialty societies. This was unexpected, especially in the context of finding minimal overall guidance addressing holistic, life-time needs.	**26**, 427
We wondered about the rationale for focussing on international guidelines only - unless we missed it.	Thank you. We have improved the rationale. Our preliminary searches revealed: (i) a paucity of local and national UK guidelines. We accept that a local guideline can be high quality and have added this to discussion; (ii) We had thought the influential 2013 RCPsych "Good Practice Guidelines for Gender Dysphoria" represented the best of UK guidance. We scored this formally during our AGREE II training (and can supply the results if wished) but they are very low quality with no linkage of recommendations to evidence; (iii) RCPsych seemed to be derived from WPATH with a suggestion of 'eminence-based' medicine in an early passage (p 9): *"The World Professional Association for Transgender Health's (WPATH) standards of care for transsexual, transgender and gender non-conforming people have informed these UK standards of care. The endorsement by several medical Royal Colleges, allied medical professional societies and service user groups sends a strong signal for the adoption of these guidelines across the UK and beyond";* (iv) Many other countries' guidelines are also derived from WPATH. Thus, given WPATH's influence, we wanted to examine the international scene. We considered our project was identifying and scientifically appraising relevant "primary sources" (the influential international CPGs) rather than "spin offs" (national and local guidelines which reference WPATH as relevant in their development). By focusing on international guidelines, we	**8-9**, 136-166

	recognise the work and influence of the expertise of professional bodies such as WPATH on UK practice and globally. We thought it would be wrong to compare WPATH and derivative CPGs as this could be seen as duplication. It was also wrong to mix one country (UK) and international CPGs as "apples and pears". International guidelines such as WHO have greater global relevance and influence than UK ones. Regarding the UK applicability of this study, WPATH has direct relevance. We are based in the UK, are interested in the implications for the NHS and thus wrote the paper for the BMJ. We decided it was prudent to focus on international guidelines in the first instance (as we did not have the resources to examine all international and all national CPGs). We have expanded on all these points in the revised introduction and methods.	
In the PPI section you indicate relevance to the NHS and getting key stakeholders from the NHS, so why not also include UK guidelines?	Thank you. We have expanded on this in the manuscript. See rationale (above) about choosing international, rather than UK guidelines. We were not confident we could properly identify and contact all international patient/ stakeholder organisations so limited the stakeholder survey to the UK where we had more comprehensive local knowledge. It is the national context in which our team is based, so the two sets of stakeholder and reviewer prioritization results might be more comparable. We conducted the study with the NHS in mind. We elaborate on this point and distinguish between the implications for the UK and other countries in the discussion.	**13**, 260 & **27**, 451-462
We wondered about the relevance of the findings fior our widespread international clinical readership.	It appears several reviewers agreed that the question is important. The topic would be of great interest to your wide readership. Globally, clinicians in primary care and all fields of medicine are likely to require greater understanding of this increasing patient group and the strengths and deficiencies of specialist guidelines. We have added implications to the discussion.	**26-28**
They would probably be more interested in what exactly is in the guidelines, than this more abstract look at the number and quality.	We agree. We are sorry we did not supply the key recommendations extracted from the CPGs which informed our interpretation. We now include Table W5 with the revised manuscript. We were unable to fulfil the protocol aim of comparing recommendations across the CPGs as there was not enough overlap for analysis. We were unable to extract key recommendations from WPATH guidance. These are major findings in of themselves that we did not express clearly. In essence, despite its influence, WPATH Standards of Care were "cryptic" (Reviewer 6's comment) and incoherent. Our work does not lend itself to recognising current WPATH guidance as reliable 'best practice' or 'gold standard'. Patients and clinicians will benefit from its next revision, if WPATH use the principles behind GRADE and AGREE II to improve quality. We hope this now clearer, fairer and evidenced.	**23-24** & Supl

On balance this seems foundational work that is better suited to a more specialised journal.	We disagree. Health equity and improving the quality of clinical guidelines for a minority population is suitable for a generalist journal and broad medical audience.	
Reviewer 1 (Ivan Florez, University of Antioquia)	**Our response**	
Authors present a review on the guidelines for gender minority-trans people. I think is an interestign question that needs to be addressed. However, I found some major isuees tha need to be addressed.	Thank you. We agree.	
1. Introduction highlights the importance of guidelines and how they are used in tainting and practice. Authors also describe that high quality guidelines is a need to better guide users (clinician, policymakers, etc).	Thank you. We agree.	
However, the narrative is a bit disconnected in some ideas. After explaining the importance of this high quality, authors state that experts are relying on guidelines that are biased by clinical observation, before an dafter studies and proxy measures, and the industry funded research. The problem with this last ideas is two-fold. First, it is not clear how from high quality authors migrate to specific limitations of "some" guidelines, in some specific cases. Also, that authors use the GRADE papers to support this idea. The GRADE approach that is cited, describe what is the concept of the quality of evidence and the foundations of the GRADE approach. The concepts described (proxy measures, before and after studies, and industry funded, of course are problem, but I might say they aren't the most important in terms of !quality of guidelines".	Thank you. We have rewritten the introduction in line with these constructive comments, emphasising for readers that quality CPGs rely on (i) evidence that goes in (GRADE) and (ii) the process of linking this to recommendations (AGREE II appraisal).	**6-9**
So, to clarify these ideas, I think authors should introduce better the concept go "quality of the guidelines", which is what they try to highlight after they mention that High quality guidelines are key. How to define high quality? Authors may describe some concepts that underpin this concept. Also, GRAde, although is associated with higher quality of guidelines, is not an approach or a tool to define it; it is an approach to assess the quality of the evidence that is selected and appraisal during the development of a guideline.	Thank you. We have rewritten the introduction in line with these suggestions.	**6-9**
2. In the same way, additional ideas/sentences area bit disconnected. For instance, "At national level, there are recognized methods to produce CPGs[2,9,10]. Health Technology Agencies are available worldwide to provide independent assurance and benchmarking[11,12]". In the first sentence, the idea is that a national level (and I suppose this means in the UK; authors should clarify) there are methods for that. I think authors should briefly explain about this methods.	Thank you. We have clarified where "national" means the UK versus all countries. We explain the UK context in the introduction, and implications for the UK and other countries in the discussion.	**8** 136-156 & **27**, 451-462
Also, the second sentence describes "HTA agencies that are available worldwide to provide…". The problem here is that there is an introduction of the concept of HTA. What is HTA? What is the relationship of HTA with CPGs?	Thank you. We have removed the reference to HTA agencies from the introduction as less relevant.	**6-9**

It is clear that in the UK, there is one single organization that develops both CPGS and HTA. This is not the case in the rest of the world.	Thank you. We have clarified and separately addressed the implications for UK and rest of the world in the discussion.	**27**, 451-462
The vast majority of organizations around the world have one or several HTA agencies that do not develop CPGs. There are some of them that do both, of course, but this cannot be used to describe an idea about the methods of CPGs.	Thank you. We have removed the reference to HTAs.	**6-9**
3. Also, the sentence that comes immediately after: "Guideline developers should respond to, and guide, research". What does this mean?	Thank you. We believe a systematic approach to evidence identifies gaps that should in turn feedback into research, e.g. in the UK there is a mechanism for NICE research recommendations to be used in NIHR funding and grant applications. Nevertheless, we have removed this sentence as less relevant.	**6-9**
Does this mean that Developers should use the research evidence (what they normally do), and also that they should provide input for future research (some kind of research prioritization tool?) . if the latter is the case, what is the relationship of this provide input for future research (some kind of research prioritization tool?). if the latter is the case, what is the relationship of this with their quality?	Thank you. Our paper is not the place to discuss these issues though we believe there is an iterative process as above. NICE guideline development groups are charged with producing 'recommendations for research', and sometimes recommends "only use in research". We have removed this.	**6-9**
4. Moreover, the following sentence is problematic: "CPGs developed by global experts and aimed at international audiences should be evidence-based, rigorous in methodology" Does this mean that a CPG to be of high quality must be developed by global experts? What does it mean to be global expert? I strongly disagree with this statement.	Thank you. We were unclear. We have removed the term 'global experts'. We have clarified that local or national CPGs may be of higher quality than international CPGs.	**25**, 401
A CPG can be or very high quality, even developed by experts that are not "global" and even if the guideline is aimed to inform a local audience only.	We agree. We have incorporated this point.	**25**, 401
Quality, and I insist on the idea that authors have not appropriately described the concept of quality, does not depend of the degree of "international experts or the scope (international audience)"	We agree. We have rewritten our introduction.	**6-9**
5. In reading the methods, I understood the interest of authors of highlighting in the methods the idea of "international guidelines"; as they focused only on these guidelines.	Thank you. We explain the rationale better in revised introduction and methods.	**8-9**, 137-166
Although, my comment on how the quality is not linked to the scope of guideline does not change, I think authors are not providing enough rationale in (introduction or methods), about why to focus on International's guidelines only.	Thank you. We agree and have addressed rationale better.	**8-9** 137-166
In fact, the development of guidelines that are international in scope have additional challenges (e.g., the implementability of the recommendation might not be easily translated among different contexts).	Thank you. We agree and have added this point. It is pertinent for gender minority/trans health because WPATH guidelines are so widely adapted. We draw attention to additional challenges and adolopment in discussion.	**8**, 153 & **27**, 461
I am not saying international guidelines should not be developed, but many times they require some efforts to contextualize in each country or settings.	Thank you. We have added this point. It is important for countries to be aware of WPATH's quality limitations when contextualizing.	**27**, 457
I mention this challenge, because authors' interest in these guidelines should be discussed as these guidelines are their	Thank you, we have strengthened the rationale.	**8-9**, 137-

scope. Moreover, I wonder, why authors focused on them? They might want to provide a good rationale in the introduction.		166
6. Why focusing on guidelines after 2010? Authors need to provide a rationale on this as well.	Thank you. We have provided a rationale. We wanted to focus on the current landscape. A five year restriction would have excluded WPATH SoCv7 (2011) which would have been detrimental. Further back, CPGs might have been out of date. The paper is important and timely as updating for WPATH SoCv8 is underway.	**10**, 189
7. The Gender Minority/Trans People population is clearly stated by authors.	Thank you.	
However, the eligibility criteria is not clear. For instance, if a guideline is on a topic that is clearly related to this population (for instance HIV), but the population is not clearly stated as targeted to this population, was the guideline considered?	We were interested in CPGs where gender minority/trans people were expressly considered for a recommendation, whatever the topic. All CPGs were considered even when gender minority/trans health was not the main subject (eg oncology communication). We do not believe that HIV is more 'clearly related' to this population than, say, osteoporosis or polycythaemia related to sex hormones. The vast majority of gender minority/ trans people do not have HIV. We would counsel against stereotyping or thinking solely about trans women and not trans men or non-binary people. Gender minority/trans people mostly have the same sorts of illnesses/ health concerns as the general population. If recommendations did not have an explicit mention of gender minority/trans people the CPG was excluded.	**10,** 182-198
8. The following sentence: "exposure/ intervention was any health intervention related to gender dysphoria or gender affirmation, or health concerns of gender minority/trans people, including screening, assessment, referral, diagnosis and interventions" gives me the idea that authors are trying to make this review fit into the commonly used PICO/PECO format, with the use of the "exposure" category.	We agree. SR of guidelines is a developing field, and the standard methodological literature has yet to catch up. We could have developed a new initialisation set, but as PECO is readily understandable this was retained.	**10,** 182-198
Methods for Systematic reviews of Guidelines, although still under development, are clearly not considering the idea of "exposure", which is only applicable to reviews interested in collecting evidence from studies that measure the "exposure", usually of observational studies, to determine risk factors or prognostic.	Thank you. As the reviewer notes, this is a developing field, so there is room for disagreement. See comment above.	
9. "Exclusion criteria" are defined as those scenarios that occur in patients/articles that you have already included, but for any particular reason, you need to exclude. In other words, exclusion criteria should not be a "negative of the inclusion criterion". Thus, studies published before 2010, should not be excluded. Same for other criteria, such as : single country, adaptations of another CPG, original research, reviews, letters, opinions, editorials, case-reports, books, and commentaries.	Thank you. We have removed these exclusion criteria from the manuscript.	**10,** 191-198
10. Not clear to me how the Agency for Healthcare Research and Quality National Guideline Clearinghouse was searched if this database does not exist anymore (this database migrated to ECRI institute)	Thank you. We explain that CM manually examined the AHRQ national guidelines clearinghouse archive that remains in the internet (not maintained since 2017)	**11**, 208

11. The use of the term: “clinical practice guidelines” as only term to identify guidelines might not be enough. Many guidelines may be labeled simply as “recommendations”, or “statements” “practice parameters”, among others.	Thank you. We have not altered the manuscript but hope the following explanation satisfies: our search strategy was checked by CM (a very experienced systematic reviewer in this area) and a British Library Science information specialist. We did come across this definitional problem, which is not unique to this SR. Therefore we kept the search strategy very wide, and searched multiple places in order to find as many includable papers as possible, adding a hand-search of journals, contact with key opinion leaders for information (they did not bring up any ‘statements’ or ‘practice parameters’ that we missed) and Google searches. If the peer reviewer knows of any includable CPGs we missed we would be very happy to include them.	**9**, 178 & **10**, 200 & Supl
Of note, this comment applies at least in many diseases; but, as I am not expert in the topic- gender minorities- this might be or not applicable to this population guidelines.	Thank you. We read a lot of full-text articles in our efforts to be cautious and did not find any examples of this being a problem.	
12. The selection process is well written and it seems to be appropriate	Thank you.	
13. Authors did a an AGREE II domain prioritization process. Although interesting, the reason for ding this was not clear and there is not a clea rationale	Thank you. We have added the reason and rationale to the manuscript. We recommend other countries do their own stakeholder prioritisations. It returns to the question of “What is good quality?” Setting quality thresholds is part of the AGREE II process. The guide is not prescriptive but gives various suggestions including: “Any decisions about how to define quality thresholds should be made by a panel of all relevant stakeholders before beginning the AGREE II appraisals. Decisions should be guided by the context in which the guideline is to be used and by evaluating the importance of the different domains and items in that context.” We decided stakeholder views should inform the work. We ran dual prioritisation collection exercises, for the internal reviewer team and external stakeholders. We kept our own rankings anonymous in order to safely reflect on our views and biases, to understand the team’s domain priorities (which might have been important in the calibrating/ instrument training process/ discussion) and to compare these to the external stakeholder respondents. As we understand the UK context and were writing for the BMJ, we felt it would be more useful to compare “like with like”. We could focus on breadth and depth with a comprehensive variety of UK stakeholder groups, rather than be too thin internationally. This would have been more important had we found CPGs that scored differentially ‘well’ or ‘badly’ by the different prioritisation. As it happened, the CPGs scored high and low on stakeholder involvement (stakeholder priority) and rigour (our priority) pari passu.	**13**, 255-258
14. Authors describe how the appraisers competed the AGREE training modules. However, there is no information on participants in the consultation knowledge about the domain, or experience with AGREE. In this survey authors asked about the domains, and people, who perhaps was the first time they heard about the tool, were scoring or deciding what domain should be prioritized. Although this is an interesting approach,	Thank you. We have added more information to the methods. Readers can access the SurveyMonkey link to see the exact wording, what queries were asked and the links to further resources including our protocol. Whilst there must be some uncertainty regarding the results, on the other hand we were writing to advocacy organisations. No stakeholder asked for clarification or more information. We expand on this point in	**13**, 267 & **19**, 327 & **25**,

more info on this might be needed to understand the results of this exercise.	limitations. We believe more could be done in future to ensure stakeholders are involved, from the generation of questions, through research participation to the dissemination of guidelines. We reference the James Lind Initiative. When published, we would wish to work with the stakeholder organisations and KOLs we contacted to ensure consistent 'messaging' of the results (e.g. in a press release) as we are conscious of community sensitivities.	398
15. In page 13, line 268, in the use of "outcomes" applies the same comment I did before about "exposure",; i dint see this is applicable in this kind of reviews. Thus, the use of primary and secondary outcomes is not, from my point of view, and appropriate way to describe the methods.	Thank you. This is how the PROSPERO website records the protocol. For the purposes of the manuscript we have now listed them in order.	**12**, 243-248
I see an interest in making this review fit into a PICO/PECO format which does not apply	Thank you. SR of guidelines is a developing field and this point is unwarranted. The format does apply, works, and our guideline review was one of several others in the PROSPERO database where protocols are assessed before being allowed to be uploaded.	
16. Authors do not prove an explanation on (some of the following are provided by the AGREE collaboration, but authors need to clearly state these methods) - how the score of AGREE work - How many assessors were, per guideline - How they managed disagreements - How they calculated final scores	Thanks. We think there is a distinction between putting enough information in our methods to allow for replication and fully explaining a standard instrument. We had provided most of this information but have amended for clarity. -The scores given range from 1-7 in 23 sections and 6 domains. -There were six assessors for each guideline. -The AGREE II instrument has capacity for inter-rater variation and calculates the final scores (as detailed elsewhere). Disagreement in scoring is not applicable here as we compensated for any differences between scorers using more than the recommended number (four). Scores were automatically generated by the myAgree platform. Each rater gives an individual score for each element of each domain. We are happy to supply the raw scores data if required. -If the reviewer means disagreement or discussion at calibration/ training stage, we took the view there was no "right" or "wrong" answer. Rather, we performed two pilots and examined the results as group learning to ensure we were fairly assessing CPGs using the instrument and discussed disagreements.	**9**, 166-174 & **13** 250-253 & **25** 396
- what was going to be the role of the results of the prioritization exercise on the analyses?	We have clarified this. The prioritisation exercise was to help set quality thresholds for what constitutes a "good" AGREE II score. It was not to change the analyses, but to focus on the domains that mattered most when interpreting the results. For further justification we refer to p10 of the most recent 2017 update PDF on the AGREE II instrument website, which refers to the following explanations: "ii) Interpreting Domain Scores. • Prioritizing one domain: • Staged AGREE II appraisal: • Considering all domain scores: • Thresholds for improvement over time." In the event (as commended by Reviewer 3, one of the AGREE II architects), we decided against choosing a quality threshold after the prioritization exercise.	**13**, 255-260 & **14** 272
17. In the discussion, if we consider the Trans population a minority, I think including this population in guidelines is a	Thank you. We agree and have added this point about equity.	**26**, 429-

matter of equity.		431
Although I am not expert in this specific population, neither in equity, I am aware of some methodological approaches to consider equity and the consideration of minority groups in guidelines. Publications from the GRADE working group and related: PMID: 28802675, PMID: 28499847, PMID: 28412464, PMID: 28389397, PMID: 29029068 , have cover this issue.	Thank you. We have read and incorporated these helpful references.	**26**, 429-435
There are several approaches to include minority populations in guidelines: 1) consider specific guidelines on these populations; *[2] (sic)* consider a health topic and develop recommendations with a strong consideration of equity issues; and 3) including specific recommendations only targeted to thesis populations.	Thank you. The reviewer refers to three approaches to developing CPGs. We were not writing CPGs, but searching for all types. We tried to include all that covered any aspect of gender minority/ trans health, with the most inclusive definitions we could muster. Nevertheless, this comment led us to review the meaning of our sparse findings and descriptive analysis. We now refer to 'complete', 'partial' or 'marginal' focus of content/ recommendations. We have added equity to implications.	**26**, 429-435
In the case of trans people, any can be applied and it seems to me authors considered all the options, but in the end they did not classify the guidelines following this (or any other framework),	Thank you. It is correct we considered all these options. We did originally label (or classify) the guidelines as full, partial and minimal, which can be viewed as short-hand for the types of guidelines the reviewer notes (i.e. 'full' is a specific guideline *on* this population, 'partial' is one with strong consideration *of* this population, like HIV, and 'minimal' is writing one or more specific targeted recommendations, like oncology communication). Now classified as 'complete', 'partial' and 'marginal', we have clarified this under data extraction in methods.	**12**, 238-241
This is helpful for analysis and for determining next steps. For instance, for some topics, different approaches might be better than the others. Authors failed to discuss on this.	Thank you. These helpful comments helped refine our classification. We have included equity in the discussion.	**12**, 238-241 & **26**, 429-435
It should not be considered the same a guideline only for this population than guideline others. Authors failed to discuss on this.	Thank you. We had discussed the difference between guidelines for this population only (transition) versus being one of several populations (HIV) but not fully enough. We have expanded our interpretation.	**26**, 422-435
It should not be considered the same a guideline only for this population than guideline on a topic that covers this population somehow.	Thank you. We agree. General CPGs that mention gender minority/trans health should not be considered the same as gender minority/trans-only ones. However, we tried to assess the entire landscape. CPGs covering any aspect of gender minority/trans health should be subject to the same quality appraisal.	
Also this has impact on the search strategy. In the first case I describe, the search strategy that has been used might appropriate, but in the latter, it might be not, and additional terms focused on diseases that may be of importance for this population need to be added.	Thank you. We agree. Our main strategy was to locate all of the first case. Nevertheless, we believe our deliberately inclusive search strategy was adequate enough for the latter (as shown by the large number of excluded CPGs, and by finding oncology and HIV guidelines at least). Although no reviewer gave an example, we accept there may be more general CPGs (say in cardiology) that we missed. We have added this as a potential limitation.	**25**, 405-407
18. Final overall comment	See earlier justification of the international focus and	

I think authors may have good reasons to focus on international guidelines, but I think the rationale is not clear in the manuscripts and I think the applicability of the work is limited when authors narrowed the scope to these guidelines. My main general comment is that authors might consider including all the guidelines (not only international), and this might make the study more interesting	applicability.	
Minor comments: 19. The following sentence is not accurate: "Clinicians have been criticised for not using methodological rigour when writing reliable evidence-based guidelines[74]". the reasons why guidelines are of low quality do not depend on clinicians. In fact, clinicians are the last to blame. The poor methodology that has been criticized is more frequently caused by experts in methodology that are in charge of the evidence search and synthesis, than by clinicians that are participating in guideline development.	Thank you. We have changed this to developers.	**25**, 416
20. NHS acronym, used in page 13, line 262, has not been previously defined	Thank you. We define National Health Service (NHS).	**8**, 145
Reviewer 2 (Anna R Gagliardi, University Health Network/University of Toronto)		
Many thanks for the opportunity to review this study, which I enjoyed reading. It addresses an important topic, appears to have been well-executed, and revealed substantial gaps that must be addressed through policy, practice and research. However, the paper would be easier to read and understand with some additional detail and clarification across all sections as described here.	Thank you. We agree.	
INTRO The first section on guidelines includes relevant key concepts but reads as a "laundry list" of topics. Consider organizing this content into distinct paragraphs and potentially re-order and re-word some of the concepts to enhance flow.	Thank you. We have rewritten the introduction.	**6-9**
For example, paragraph one: introduce guidelines and how they support high quality health care delivery; paragraph two: despite widely recognized principles and methods for developing sound guidelines, current research shows that guidelines on various topics lack x, y and z OR scored poorly when assessed for methodological quality [cite very recent studies that assessed guideline quality]. This finding emphasizes the ongoing need to appraise guidelines on various topics to ensure that patients, family/caregivers and clinicians have access to the best evidence-informed care.	Thank you. We have rewritten the introduction with these points.	**6-9**
Please also address some grammar and clarity issues. For example: "At national level, there are recognized methods to produce CPGs." Should this be "levels"? Or would it be more appropriate to say globally-recognized approaches/methods?	Thank you. We have removed this.	
What does this mean: "Guideline developers should respond to, and guide, research." Use active voice, which is easier to read (e.g.Organizations have produced globally-recognized	Thank you. We have removed this comment. We use more of the active voice within the article.	

methodological guidance for developing robust guidelines), and do so throughout (e.g. We searched six databases…)		
There are also some grammar/clarity issues in the next section on gender minority/trans people. For example: "Despite efforts to depathologise [what, exactly?],…" and "Gender minority/trans people may experience more mental health…[more than who?].	Thank you. We have removed this.	
Introduce AGREE in Methods, not Introduction.	Thank you. We have revised the manuscript; it now mentions AGREE II in the introduction, but expands on the detail and justification in the Methods.	**6**, 109 & **9**, 166-174
Blend aim/purpose statement with previous paragraph rather than including this statement in a separate section.	Thank you. Done.	**9**, 157
Emphasize that, while WPATH guidelines are available, no prior study has investigated the number and quality of guidelines to support the care and well-being of gender minority/trans people. Thus, it is not known if guidelines are available to persons, family/caregivers or clinicians that would optimize care, and health and well-being. The purpose of this study was to identify and appraise the quality of guidelines on…	Thank you. We have added this to the introduction.	**8**, 156
METHODS Start with an Approach or Research Design section that provides the reader with a high-level sense of the methodological approaches used, justification for those approaches, and references for those approaches and for relevant reporting standards for the systematic review and for reporting electronic search strategies (i.e. PRESS).	Thank you for this very helpful suggestion. Done.	**9**, 162
Justify why Jan 1, 2010 was chosen as the start date.	Thank you. We have added the rationale. We wanted to focus on the current landscape. A five-year restriction would have excluded WPATH SoCv7 (2011) which would have been detrimental. Further back, CPGs might have been out of date. The paper is important and timely as updating for WPATH SoCv8 is underway.	**10**, 189
How did you establish or decide who the international opinion leaders were? There are multiple methods of identifying opinion leaders.	We identified Key Opinion Leaders via reviewer knowledge of published literature from previous SRs (DC, SD) and have added this to the methods.	**11**, 215
For data extraction, suggest you first report the descriptive data extracted, and then introduce and describe the use of AGREE	Thank you. Done.	**12-13**
Here you introduce a key element of data you extracted, the recommendations, and state that you assessed it as whole, partial or minimal.	We have revisited and clarified this. It is now "complete, partial or marginal focus of content/ recommendations."	**12**, 238-241
If you did examine guideline content in this way, then it should be recognized in the Introduction's purpose statement, and far more detail is needed to explain who did this work and if content was assessed independently, explain how the content was extracted (e.g. only bullet point recommendations) and	Thank you. We have added more detail. Data extraction of key recommendations was performed by two independent reviewers and was entirely straightforward for 11 CPGs. All six authors attempted to extract WPATH recommendations. We have re-written the introduction and clarified the data extraction of the	**12**, 230-241 & Supl

from where in the guideline, and define whole, partial and minimal and how that was assessed.	CPG recommendations (including an additional Table W5). We have changed the description to "complete, partial or marginal focus of content/ recommendations" (a post protocol interpretation having started inclusively).	
Outcomes section should follow data extraction for continuity, then conclude with Patient and Public Involvement.	Thank you. The outcomes section now follows data extraction.	**12**
Regarding Outcomes, the number of guidelines on this topic, while important, seems similarly important to the other outcomes; suggest you simply report outcomes without designating them as primary or secondary.	Thank you. Done. We agree, but outcomes had to be described like this for the PROSPERO webform.	**12**, 243-248
Regarding Patient and Public Involvement, it is not clear why they prioritised the AGREE domains, or what was done with this information.	Thank you. We have clarified (as above, Reviewer 1 point 13) and made clearer in the text. AGREE II generates scores, but presently there are no data to link CPG scores with outcomes. At the start of the project, the team discussed how to set thresholds for "good quality". The AGREE II instrument suggests consulting with relevant stakeholders (optional). We felt it would be appropriate to find what domains stakeholders place most value in, so created the prioritisation exercise. The investigating team also performed the same ranking task so we could compare groups. The results illustrated a difference in priorities. We made the decision not to impose quality thresholds, so as to not give more weight to our own views of "good quality" over that of stakeholders.	**13**, 255-258
RESULTS. Use sub-headings: Search Results, Guideline Characteristics, and then a sub-heading for each outcome (i.e. whole, partial or minimal should be separate section pertaining to content and consistency)	Thank you. We have added subheadings as suggested.	**14-24**
At this point, it's not clear why you compared domain prioritisation; it does not appear germane to the other outcomes; consider excluding	Thank you. We now explain this in more detail. It is not an outcome in of itself, but a way to set a threshold for 'good' quality. After comparing domain prioritisation we decided not to set a threshold (as approved by Reviewer 3, one of the architects of AGREE II).	**13**, 255-258 & **14**, 272
The fact that you assessed consistency of recommendations and patient-facing material should be both mentioned and described in Methods	These assessments were mentioned in the methods, but maybe not clearly enough. We have added further description.	**14**, 235-238 & 247-248
DISCUSSION Unclear what is meant by "it was impossible to reliably discern key…" because it's not evident what details of the Results this refers to.	We apologise for not being clear. We now expand on this in results. We have added Table W5 with all key, clearly discernable recommendations from the CPGs. Six reviewers independently extracted what they thought were key recommendations for WPATH. Our views ranged from 0 to 168 with very little agreement. We are happy to supply cross tabulations of all the statements extracted by the six reviewers, but hope the new description explains this better.	**23-24**, 366-379 & Supl
This first paragraph, which is meant to briefly summarize key findings, omits some of study's findings With respect to implications, rather than reiterating key findings, choose two or	Thank you. We have improved the discussion in this way.	**24** & **26-**

three key findings and elaborate on what could be done in policy or practice to address or implement the findings, and draw on and reference relevant literature to support your recommendations		**28**
PRISMA. The figure requires editing as arrows are clearly misplaced	Done.	Fig 1
Reviewer 3: Gene Feder (Centre for Academic Primary Care, Bristol Medical School, University of Bristol)		
This manuscript reports a comprehensive systematic review of (relatively) current international clinical guidelines that include recommendations or standards for the care of trans/gender minority people. The reviewers have judged the quality of the 12 guidelines using the 6-domain AGREE II appraisal tool and consulting UK stakeholders about which of the AGREE II domains they prioritise.	Thank you.	
A major finding is that the scope of the guidelines is confined to HIV/STI prevention or management of transition. The quality scores have a wide range and heterogeneity and the reviewers are wise not to specify quality score thresholds, although there is a pattern: guidelines that include recommendations about HIV/STI are higher quality and those focusing on transition are lower quality.	Thank you. We have added these clearly expressed points.	**3**, 61 & **24**, 387
The authors' discussion is consistent with their findings and their pitch for better quality, wider scope clinical practice guidelines for gender minority/Trans people is well made.	Thank you.	
Needless to say, clinical guidance around transition is controversial. The close attention to avoidance of bias in this systematic review (including exceeding the number of independent reviewers recommended in the AGREE II manual) is crucial in the current debate about the medical response to gender dysphoria/incongruence.	Thank you. We have added this point about close attention to avoidance of bias into strengths. If published we feel this would be a useful point for any press release.	**25**, 395
Unusually for me, I have no suggestions for improving the manuscript. Not only is it well written, but it has been forensically proof read.	Thank you. We are very grateful for this positive review from one of the architects of AGREE II.	
Reviewer 4 (Yaolong Chen, Lanzhou University)		
The authors evaluated CPGs for the assessment and health care of gender minority/trans people. This is an interesting topic in recent years. The authors included twelve guidelines in their review. They concluded that there is a need to improve the quality of healthcare advice for gender minority/trans people by producing evidence-based, methodologically sound, independently assured guidance with better stakeholder involvement and informative patient-facing decision aids.	Thank you. We agree this is an interesting, current topic.	
Overall, this is a descriptive study with clear and well written. The authors followed the standard methods, including PRISMA checklist, flow diagram and registering with the PROSPERO platform.	Thank you.	
However, the topic of the article is novel, but the content is presented in much the same way as other evaluation guidelines using AGREE II, with little innovation.	Thank you. We agree the topic is novel. We believe there is innovation which we have clarified in the manuscript: (1) the stakeholder prioritisation, (2) examining the content within the	**13** 255-260

	guidelines (protocol aims 3-5) which we have highlighted more clearly through adding Tables W4 and W5.	& Supl
Major comments: 1. The first paragraph of the introduction is somewhat redundant. I think it is sufficient to state what the clinical practice guideline is and what its role is.	We have rewritten the introduction	**6-9**
2. The authors do not state in the introduction section that it is not clear that the quality of current guidelines on gender minorities/trans people, there is therefore no mention of the necessity for this study.	Thank you. We have mentioned "quality of current guidelines on gender minority/ trans health is unclear" thus justifying the necessity.	**8,** 137
3. The authors did not fully follow the research protocol registered at PROSPERO, e.g. search strategy.	We disagree. The search terms listed in the protocol were all used in the final search strategy, plus some additional terms. Therefore, the searches were improved. We have identified the minor protocol deviations more clearly.	**11**, 213
4. The authors did not follow their inclusion criteria. As stated in line 192, they would like to include the guidelines based on the review and assessment of available clinical evidence. However, in the guidelines they incorporated, I saw some guidelines without systematic reviews.	Thank you for the comment. We disagree. We did follow our inclusion criteria. We apologise if this was not clear and have added a point about variation in CPG definitions in the introduction to explain. The protocol did not insist upon CPGs having formal SRs. It states: "A clinical practice guideline (CPG) is defined as a *systematically developed set of recommendations* that assist practitioners and patients in the provision of healthcare in specific circumstances, produced *after review and assessment of available clinical evidence*. A CPG or part thereof, will be included if it fulfils all of the following criteria: *evidence-based with some documentation of the development methodology*" Preliminary searches showed a paucity of SRs in the field. In addition, some CPGs used a mixture of SRs and expert consensus. We wished to be inclusive. Thus, the definition we used was not reliant on CPGs being informed by an SR. The documents needed to include some sort of methodology and linkage to evidence: i.e. the recommendations needed to be *systematically developed*. This could have been getting a panel of experts together (e.g. Ralph), having discussions or voting systems, together searching the literature (perhaps in different sub-sections / subgroup in CPG development committee). We were disappointed to find that so few guidelines had SRs. We have emphasised this finding more in the discussion.	**6,** 98 & **10**, 182 & **24**, 387
5. The authors did not state in the purpose that the analysis and comparison of the recommendations are to be made, but they did in the results section.	Thank you. We did mention this but maybe not clearly enough. We have emphasised it better in the methods.	**12**, 235, 247
Minor comments: -Abstract □ Line 90, six lower-quality CPGs concerned transition-specific interventions (overall assessment scores 11-56%)… I can't find this result from the Results section.	Thank you. We had tried to avoid repetition between text and tables in results. We have now added the overall assessment scores to the text of the results (figures are found Table 2).	**19**, 328
-Introduction □ It is recommended that some of the well-known knowledge of clinical practice guidelines be removed from the background section□	Thank you. Other peer reviewers suggested more discussion about quality assessment. We have rewritten the introduction and removed some well-known knowledge of CPGs.	**6-9**

-Methods □ Line 213, a clear description of whether it's Google or google scholar because on PROSPERO it's google scholar?	Thank you. We confirm this was a mistake. We should have written Google in the protocol. We wanted to use this search engine to identify potential CPGs in the grey, not scholarly literature. We have added explanatory text.	**11**, 211-213
□ Line 214?the fact that NGC has been shut down in 2017, how do you get guidelines from NGC?	Thank you. We explain that CM manually examined the AHRQ national guidelines clearinghouse archive that remains in the internet (not maintained since 2017)	**11**, 208
□ Line 218?the journals searched are listed here, but there are no instructions on the PROSPERO?	Thank you. This search was added after registration. We have noted this in the methods.	**11**, 209
□ Line 248?how overall quality is evaluated and calculated?	We have added information to methods about how the AGREE II tool works.	**9**, 166-174
-Results □ Line 283, 1781 citations were identified… however in Figure 1, 1787 citations were identified, please check which one is correct.	Thank you. We have corrected the typographical error.	**14**, 279
□ Line 303-306, the authors give a range of scores for each domain, suggesting that an average score for each domain can be given for all guidelines.	The range is derived from Table 2. Scores are calculated by the AGREE II instrument for each CPG. The range was mentioned to give an illustration of the wide variation in scores, rather than suggest domain averages could/ should be calculated across the guidelines. We have altered the accompanying text.	**19-20**, 328-340
-Discussion □ Line 384, What are the potential implications of this study for high-income countries and low- and middle-income countries, respectively? Could you discuss this?	We focused on the implications for the NHS. We are less confident speculating about implications for high versus low and middle income countries, but have added some points for other countries in discussion.	**27**, 457-461
□ Line 416, please add the full name when it first appears, including NICE?SIGN?MAGIC.	Done.	**8**, 148
-Figure and tables □ The lines in Figure 1 are messy, please save it to a non-editable format.	Done.	Fig 1
□ Please add the full name of the abbreviation below Figure 1.	Done.	Fig 1
- Supplementary materials □ Page 40, line 17, as stated in the search strategy, the search start date is January 1, 2010, so why start with 2008 here?	Thank you. Inclusions were 2010 onwards so the searches would have picked up everything relevant.	Supl
□ Page 40, line 30, as I know, in MEDLINE, CPG has three MeSH words, ie, guideline, practice guideline and guideline as topic.	The search terms we used incorporated all of these.	
Reviewer 5 (Emma Rush, patient reviewer)		
Are the issues identified relevant and important to patients and/or carers? This paper is a systematic review, and its objective is identified as being: To identify and critically appraise published international clinical practice guidelines (CPGs) for the assessment and health care of gender minority/trans people. At the outset the expectation is therefore wide-ranging, and that the review will cover two stages, the assessment process and then the ongoing health care of gender minority or trans people.	Thank you. We have clarified the aim as 'healthcare of gender minority/trans people' as we wanted to capture everything. We do not want to split matters as if there was a simple, linear, two-stages of assessment and then ongoing healthcare.	**3**, 45 & **9**, 158

It goes on (l 95) to recognise a lack of 'high- quality guidance, especially relating to mortality, quality of life, sizes of benefits and harms, and patient facing material'	We agree.	
Many patients and carers are, certainly in the UK, aware of this lack and a focused approach to throughout-life health care and as volumes of patients within the NHS increases there is a real need for some consistent guidance to clinicians across specialisms on the specific risks to, and means of addressing and treating the gender minority /trans population.	Thank you. We have added this point to the discussion, as it is also an equity issue.	**28**, 469-471
From a patient's point of view, referring to participants as 'trans identifying' is misplaced (page 4/page 10). The point about being trans for many people is that that is their identity it's not a transient state in which they 'identify as' and adding 'identifying' questions the authenticity of their experience. They are trans. I recommend that the reference throughout is to 'trans people' not 'trans identifying.	Thank you. We have removed 'identifying.'	
Do you think the level of patient/carer involvement in the study could have been improved? If there was none do you have ideas on how they might have done so? Reference is made (page 13 l 262) to fifty-two stakeholder groups being consulted about the prioritisation exercise for the AGREE domains. It isn't clear whether that exercise went out beyond the groups to the patients they might represent and may be worth clarifying briefly, perhaps by noting the number of responses to the SurveyMonkey questionnaire here in the text of the review.	Thank you. We had 19/52 replies (a 39% response rate) which we report and believe is a good, and typical, response to a query of this sort. We do not know if the link was circulated further to any groups we had not identified.	**19**, 324
. It would also be interesting to compare and contrast in the text (even if briefly) the different priorities in Table W2, to involve patients/ patient representatives further in the text.	Thank you. We did mention this but as the stakeholder/rigour of development quality scores tended to be high or low hand-in-hand, we felt it was stronger to mention the absence of patient facing material before starting the discussion. We think the absence of patients/ patients' representatives is highlighted. We have added a patient implications section to the discussion, highlighting the need for stakeholder involvement. We did not go further in terms of patient/ carer involvement. The work was first presented at WPATH (November 2020). We intend to report to the stakeholder organisations as part of dissemination.	**24**, 381 & **19**, 333 & **28**, 463-474
Is the treatment or intervention suggested or guidance given something which patients/carers can readily take up? or does it present challenges? It would be interesting, even though this is a systematic review rather than description of a treatment or intervention, to encourage current trans / gender minority patients who might be in the NHS system within the UK to contribute where they are comfortable to do so to any research being undertaken by their clinicians. Reference is made to RCTs and long term observational studies on page 21 and perhaps one of the needs for these to be a success, and to contribute data for the future health of trans /gender minority patients is to use this paper as a positive call to contribute to patients and stakeholders. If CPGs don't exist because there is insufficient data, the new generation of patients coming into the NHS are	Thank you. We agree with these points that have been added to the discussion.	**28**, 463-474

those who can contribute to the future of this field of medicine.		
Individual queries: Page 8Ls 136 -138 Why was this this definition of trans people chosen over more recent, stakeholder-driven definitions? Were stakeholder groups consulted on the use of this definition?	Thank you. We appreciate that other definitions exist, and terminology develops rapidly (including for various medical words/ concepts associated with CPGs for gender minority/ trans health). Stakeholder groups were not consulted on the definition. It was developed with reference to WHO, the highest international health body, to communicate concepts to a generalist, global, predominantly medical audience who may not understand terms like gender identity/ gender expression, or define them the same way across languages/ local contexts/ cultural understandings. As the main readership is clinical, a unifying, somewhat medical definition seemed prudent.	
L 151 It would be useful to quote figures here – for example The Tavistock provides figures for the increase in referrals to their service for young people, which might show the number of people presenting at the beginning of their health care lives who will subsequently require ongoing primary and secondary care.	Thank you, we have rewritten the introduction. We believe the article is long enough without focusing on young people, as all adult gender minority/trans people who transition medically will also require continuing care. Putting results into context might be the focus of an accompanying editorial (e.g. maybe by a Professor of General Practice, such as Reviewer 3).	**6-9**
Page 9 The reported poor population health and difficulties with accessing appropriate healthcare. Where is the reference for this statement please?	We have removed the statement. It was intended to sum up the preceding referenced points about access and health risks.	
Page 17 l 352 what is snowballing?	Removed.	
Page 17 l 336 Can a conclusion or recommendation be drawn from this, for example that this, given that it was a stakeholder priority must be a priority for future CPGs in this area?	We agree this must be a priority in future CPGs, especially as it was a stakeholder priority. We had made this point but maybe not well enough. We have added implications for patients to discussion.	**28**, 463-474
Page 20 Meaning of the study: possible explanations and implications for clinicians and policymakers This paragraph to line 405 is confusing to read.It would be easier if key findings were in headed paragraphs relating to Clinicians; Policymakers and Patients with an overall conclusion at the end.	Thank you. We have rewritten this, subdividing the implications, and included patients.	**28**, 463-474
Line 405 – what does 'further develop a learning culture beyond empiricism' mean? That clinicians should not try things out with patients on a case by case basis and base patient treatment exclusively on evidence or CPGs where they exist?	Thank you. We have removed this comment. Patients should have individualised plans. However, doctors are obliged not to experiment on a case-by-case trial; they should work in teams and test their treatments, both generating and following evidence. Otherwise they may be doing more (long term) harm than they realise from their (short term) grateful patients. We have not expanded on ethics, nor referenced the 2020 Cumberlege report, but these might be covered in an accompanying commentary.	
Surely one of the difficulties in this field of health care is that each case presents as new to the clinician with many clinicians recruited into the field from others, rather than having the privilege of spending their entire working careers in this area of medicine.	Thank you for this point. The authority gained from working in a field for a long time (especially where definitions, diagnoses and numbers appear to be in flux) does not guarantee a doctor is doing good, or continuing to do good. Understandings and standards might change. If clinicians come in anew, it is even more important to have high quality CPGs.	
Page 21 Conclusion I feel patients would benefit from seeing this final conclusion include a recommendation here, even in simple terms such as	Thank you. We find this is a good point, and something to work with the community/ stakeholders in a positive way. We have added this recommendation.	**29**, 490

the need for further evidence-based work to take place in preparing CPGs that cover the gender minority/trans person's holistic care.		
The conclusion on page 5 is much clearer and a great call to action.	Thank you.	
Overall, can I please ask, is the recommendation that specific CPGs for trans care should be improved across the different aspects of an individual's healthcare, or that in all CPGs, for example in disease-specific guidance, trans care should become an element of that guidance?	Thank you for this good question. It is not an either/or call to action, but ideally both: (1) CPG producers creating transition-related or trans health focussed recommendations ought to improve quality, and (2) CPG developers across healthcare ought to consider whether trans patients may have unique needs (NICE does this with Equality Impact Assessments). We have clarified this in the conclusion.	**29**, 490
Reviewer 6 (Vivienne Bachelet, Universidad de Santiago de Chile)		
I appreciate the opportunity that the journal has given me to review this paper. I find this systematic review of CPGs for gender minority and trans people an interesting and important research project, and the results should be published.	Thank you. We agree that it's interesting, important and should be published.	
My main recommendation is to cut as much as possible unnecessary references. For some reason, medical writing has lost its flow—each statement having to be supported by "evidence," which is pretty arbitrary, and, while I recognize that journals and editors may be responsible, it does not make it into good writing. Remember David Sackett's writing style?	We are grateful for this suggestion to improve writing style. We have cut references, although there were additional suggestions and sources recommended by other peer reviewers.	
Introduction I find the way the first paragraph is written sounds too mechanical. There are way too many references not needed for obvious things. Please write this out with your own words to make reading pleasant, and cut some references	Thank you. We have rewritten the introduction.	**6-9**
The point to be established is that CPGs are important and have limitations. A couple of references to the SRs are enough.	Thank you. We have made this point.	**6**, 99
In the following paragraphs, I would recommend using references only to support quantitative statements (e.g., pg 10, lines 157 to 163) and important ideas that are not your own. For minor, tangential statements that are pretty much common knowledge, there is no need for supportive references.	Thank you. We have removed some references but added others.	
Another style suggestion is to bring together sentences so that reading is made more effortless (e.g., pg 10, line 170 to 172 where a connector is warranted).	Thank you. We have tried to make reading more effortless.	
The remark on AGREE II in pg 10, lines 175 to 179, seems out of place here. I think it should be introduced before zooming into CPG in your population of interest and their critical appraisal. Maybe change the order of the ideas…just a thought.	Thank you. We have changed the order to introduce AGREE II before population of interest.	**6**, 111
Furthermore, I would be interested in knowing a bit more about why there are reservations (reference 37). Is the mention of WPATH necessary for this review? If it is, then this notion should be developed further, including the potential critique. Remember, many of the readers, like myself, are not experts	Thank you. We have explained why WPATH is of central importance, explained existing critiques and why its quality might have implications for practicing professionals globally.	**8**, 140-143

in transgender issues. More likely, we know nothing and look forward to reading your paper to introduce ourselves to the topic. It WPATH is not essential, then delete this whole concept. You are the experts.		
Methods Pg 11, line 193: Why does the eligible population of CPG begin after January 1st 2010? Repeat mention in line 106 but no explanation.	Thank you. We have added the rationale. We wanted to focus on the current landscape. A five year restriction would have excluded WPATH SoCv7 (2011) which would have been detrimental. Further back, CPGs might have been out of date. The paper is timelier as updating for WPATH SoCv8 is underway.	**10**, 189
On the search: Why did you not include LILACS in your databases? Not that I think that it will make much of a difference, but systematic is systematic.	Thank you. We have added this database that was overlooked at protocol stage although no more full papers were found.	**11**, 203 & Fig 1
Pg 14, line 266, please explain that the link leads to the survey.	Done.	**13**, 267
On the survey, and considering that in the discussion section you say that one of the strengths of the study was "snowballing," please explain in the methods section how you used this sampling method, or, better yet, whether this was the sampling strategy done (it appears not). I seem to understand from your paper that you just contacted as many stakeholders as possible because you do not provide a report on your sampling strategy for the key opinion leaders. You only say you "approached" them (pg 11, line 223 to 224.	Thank you, we have explained this better in methods. There were two separate exercises: (1) for international key opinion leaders, identified through published works, one email invitation & reminder. DC has good knowledge of the field having previously done SRs on gender minority/ trans health; (2) for stakeholder prioritisation, identified through local knowledge and Googling by the whole team, two emails with a link to the survey. Although we invited recipients to pass invitations onto their networks, we agree 'snowballing' (sampling) is wrong, so the term is now deleted.	**11,** 215 & **13**, 262
Furthermore, the word "snowballing" has an entirely different meaning that you do not want to include in your paper (for more, Google).	We agree. The term has been removed.	
Results Pg 17, lines 331 to 334. I understand that the WPATH guidelines may have been cryptic or confusing. Is that it? I do not understand this: "After discussion, it was decided not to revisit inclusions post hoc but to abandon this protocol aim." So, it appears something is going on with WPATH, but I do not know what from reading your paper…I am intrigued, in any case. Maybe their recommendations are not a CPG but just a laundry list of things to do or to not do? Who knows…this is not my field.	Thank you. We have clarified the difficulty in results. We believe that WPATH SoCv7 is a CPG: it certainly presents itself as such (or evidence-based 'standards of care'), but the problem is that there are no clear key recommendations. Nor are there clear standards against which an individual or service could compare themselves. There is a lot of 'flexibility,' which on closer inspection becomes incoherent. Thus the document is not even a 'laundry list' (as you suggest). Between the six of us we could not identify the 'list'. This should be easy to fix, if WPATH would issue v8 with a 'key recommendations' section as we advise in discussion.	**23-24**, 367-379 & **27**, 446
Discussion. Please delete your mention of "snowballing." You did not conduct snowball sampling for this study.	Done.	
An explanation was found for the WPATH ontroversy! I correctly second-guessed the underlying issue when reading the previous sections.	We apologise for the reviewer's difficulty. The preceding sections are now clearer with extra explanation in the text and Table W5 (CPG key recommendations) which will inform readers better.	**23-24**, 367-379 & Supl
Once again, please go through your writing style, and cut	Thank you. We may have overdone the references because we	

unnecessary references.	are conscious of sensitivities in this area of research. We have removed many. We are happy to prune more knowing we can supply them if asked.	
Conclusion. The first sentence does not stem from the results as it is a declaration of desirability. The second sentence rings true after reading your report, but a one-sentence conclusion section seems insufficient. I would drop this section altogether and take the "underserved" concept to the latter part of the discussion.	Thank you. We have reworded this section.	**29,** 487
Minor observations Pg 8, line 120 Awkward wording (including by reducing between-clinician variation).	Reworded.	**6**, 94
Pg 16 line 298 rewrite the range using the word "to".	Done.	**14,** 293
Reviewer 7 (Alfonso Iorio, McMaster University)		
This is an interesting piece of evidence, exploring a very timely and relevant topic.	Thank you. We agree that it's very timely and relevant.	
Exploring the representation and quality of evidence around gender defined minorities and gender incongruence is an excellent way of prompting new researcher wherever there are gaps.	Thank you. We agree.	
Technically, the work was well conducted and reported with plenty of details.	Thank you.	
Here are some simple, broad suggestions for improvement. 1) Whilst fully understanding the underlying motivation for the SR, and the need to provide education to the readership in the specific field, the authors should consider focusing the information provided in the background section to what is relevant tounderstand the present work.	Thank you. We have refocused the information in the background to concentrate more on 'what is high quality?'	**6-9**
Similarly, the discussion should focus more on the results and methods of the review and less onthe general topic. Maybe an accompanying editorial would be more appropriate to broaden the scope of the conversation.	Thank you. We have rewritten the manuscript to focus more on methods and results. If this were published, we think the suggestion of an accompanying editorial to broaden the scope of the conversation is good.	**24-29**
2) I have one main concern on the study design, which is on one side the decision to exclude single country guidelines and on the other side to include only UK based stakeholders	Thank you. We have improved the rationale. Our preliminary searches revealed: (i) a paucity of local and national UK guidelines. We accept that a local guideline can be high quality and have added this to discussion; (ii) We had thought the influential 2013 RCPsych "Good Practice Guidelines for Gender Dysphoria" represented the best of UK guidance. We scored this formally during our AGREE II training (and can supply the results if wished) but they are very low quality with no linkage of recommendations to evidence; (iii) RCPsych seemed to be derived from WPATH with a suggestion of 'eminence-based' medicine in an early passage (p 9): *"The World Professional Association for Transgender Health's (WPATH) standards of care for transsexual, transgender and gender non-conforming people have informed these UK standards of care. The endorsement by several medical Royal Colleges, allied medical professional societies and service user groups sends a strong signal for the adoption of these guidelines across the UK and*	**8-9**, 137-166 & **13**, 260

	beyond"; (iv) Many other countries' guidelines are also derived from WPATH. Thus, given WPATH's influence, we wanted to examine the international scene. We considered our project was identifying and scientifically appraising relevant "primary sources" (the influential international CPGs) rather than "spin offs" (national and local guidelines which reference WPATH as relevant in their development). By focusing on international guidelines, we recognise the work and influence of the expertise of professional bodies such as WPATH on UK practice and globally. We thought it would be wrong to compare WPATH and derivative CPGs as this could be seen as duplication. It was also wrong to mix one country (UK) and international CPGs as "apples and pears". International guidelines such as WHO have greater global relevance and influence than UK ones. Regarding the UK applicability of this study, WPATH has direct relevance. We are based in the UK, are interested in the implications for the NHS and thus wrote the paper for the BMJ. We decided it was prudent to focus on international guidelines in the first instance (as we did not have the resources to examine all international and all national CPGs). We have expanded on all these points in the revised introduction and methods. Regarding stakeholders we were not confident we could properly identify & contact all international patient/ stakeholder organisations so limited the survey to the UK where we had more comprehensive local knowledge. It is the national context in which our team is based, so the two sets of stakeholder and reviewer prioritisation results might be more comparable.	
I am afraid this choice was unfortunate, for a series of consideration. First, the social acceptance and consequent health care system coverage of gender diversity related issues vary significantly among different countries, which is likely limiting a lot the space for international/multinational guidelines. Therefore, there are many more country-specific guidance documents (18) than international ones (12).	Thank you. We have added this important point to the discussion. We have explained our rationale for choosing international rather than country-specific guidance in the introduction, as many national CPGs are WPATH derivatives. Finally, whatever the social acceptance and healthcare coverage, the issues about 'what works, for whom and when?' should (mostly) be a matter of evidence.	**25**, 402
Not exploring the country level specific guidelines may well determine losing the most important content in the field, including what could be relevant to UK. Particularly in view of the well determine losing the most important content in the field, including what could be relevant to UK.	Thank you. See above. What we found in preliminary searches and have clarified in the introduction was that UK clinical practice appears to be influenced by WPATH as a "key" source. We have commented on a lack of national CPGs as a potential limitation.	**25**, 401
Particularly in view of the well developed methodology to localize, adapt or even adolopment (following the GRADE terminology) there is no a priory robust reasoning in support of excluding single country guidelines.	Thank you. Our rationale about international CPGs has been strengthened. We now mention adolopment in the discussion. We encourage future research (including single-country guideline appraisal) in this area.	**27**, 461 & **28**, 477
Also, the choice of limiting the stakeholders to one single country suggests, as somehow discussed by the authors, that they are interested in a UK relevant perspective (which is similar, in a way, to planning/ developing a country specific guideline), which would have not been included in the present review, if exisiting. I am not sure how this conundrum could be	Thank you. We have expanded on how UK and international CPGs in this area are, in our view, interrelated.	**8-9**, 137-166

solved, but to me, this is a major limitation of the current work.		
3) My expertise in the guideline field, so I proposing this comment more to offer the authors a chance of clarifying. They state (Page 8, 145 and ss) that the latest definition for gender choice related health problems is incongruence, and that this is replacing the concept of dysphoria. However, in the rest of the paper, they continue to refer dysphoria. This seems a bit counterintuitive and requires some clarification; either the authors judge that incongruence is not yet an accepted term, and is better not used, or I would think science in the field would benefit from this paper adopting the latest definition.	Thank you. We have clarified our introduction on gender minority/trans health and amended the text to no longer focus on gender dysphoria.	**7**
4) Many references are not uniquely identifiable (e.g. refs 7 and 8); please use urls pointing directly to a specific page, and indicate date of last access (using the BMJ mandated format).	We have revised the references where feasible.	Ref

International Clinical Practice Guidelines for Gender Minority/Trans People: Systematic Review and Quality Assessment

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Compliance with Ethical Standards

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Structured abstract

Objectives: To identify and critically appraise published international clinical practice guidelines (CPGs) for the assessment and health care of gender minority/trans people.

Design: Systematic review and quality appraisal of CPGs using AGREE II tool.

Setting: Six databases and six CPG websites were searched, and international key opinion leaders approached. UK-based stakeholder and reviewer AGREE II domain prioritisation was performed.

Participants: Adults and/or children who are gender minority/trans-identifying with no exclusions due to comorbidities, except differences in sexual development (intersex).

Intervention: Any health-related intervention connected to the care of gender minority/trans people, including screening, assessment, referral, diagnosis and treatments.

Main outcome measures: Number of international CPGs addressing the health of gender minority/trans people, AGREE II scores, information on estimated changes in mortality or quality of life (any measure), consistency of recommended interventions, and appraisal of key messages for patients.

Results: Twelve international CPGs addressed gender minority/trans people's healthcare as a full (n=5), in part (n=4) or minimal (n=3) component of guidance. A wide range of AGREE II quality scores was found whichever domain was prioritised; stakeholder involvement (favoured by UK stakeholders, 14-93%), or methodological rigour (favoured by reviewers, 17-87%). Five higher-quality CPGs described trans people as a key population for HIV and other blood-borne infections (overall assessment scores 69-94%). Six lower-quality CPGs concerned transition-specific interventions (overall assessment scores 11-56%). No international CPGs dealt with primary care, mental health, or longer-

term medical issues. There was little and conflicting information on estimated changes in mortality and quality of life. The consistency of recommendations could not be examined due to lack of clarity and overlap. No CPG provided key messages for patients.

Conclusions: Gender minority/trans people are ill-served by present international guidelines which are limited to the HIV epidemic and transition. A paucity of high-quality guidance, especially relating to mortality, quality of life, sizes of benefits and harms, and patient facing material must be addressed. To deliver equitable, high-quality healthcare that gender minority/trans people deserve, future guidelines must be based on evidence from systematic reviews, incorporating patient values and preferences as well as considering clinical and cost-effectiveness. Unbiased processes, independent external review and health agency assurances are needed, so that individuals and policy makers can make properly informed decisions.

Trial registration: The protocol was prospectively registered with PROSPERO (CRD42019154361)

Summary Box

What is already known on this topic • Unbiased, high-quality, evidence-based international clinical practice guidelines (CPGs) improve health outcomes. • More gender minority/trans people are seeking and receiving transition-related care and have continuing health needs.
What this study adds • First systematic review to use a validated quality appraisal instrument to assess all international CPGs addressing gender minority/trans health. • Five higher-quality CPGs (overall AGREE II score 69-94%) focus on gender minority/trans people as a key population for HIV and other blood-borne infections, whereas six lower-quality guidelines (overall AGREE II score 11-56%) focus on transition interventions. None focus on primary care, mental health, or long-term medical issues. • There is a need to improve the quality of healthcare advice for gender minority/trans people by producing evidence-based, methodologically sound, independently assured guidance with better stakeholder involvement and informative patient-facing decision aids.

Introduction

Clinical practice guidelines

Evidence-based practice integrates the best available research evidence with clinical expertise and the patient's unique values and circumstances[1]. Clinical practice guidelines (CPGs) are "statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options"[2]. Recommendations are used by and for patients, alongside professional judgement, directly or within decision aids, in training and practice. High-quality CPGs are necessary to guide clinicians and policy makers[3], to improve the quality of care[4], thereby affecting patient safety[5] and outcomes, including by reducing between-clinician variation[2]. Healthcare experts, specialist societies and patient-interest groups have often relied on guidelines that are potentially biased by clinical observations, short-term 'before-and-after' studies, proxy measures and industry-funded research[6,7]. Methodological improvements have included transparency, rigour, independence, multidisciplinary input, patient and public involvement, avoidance of commercial influences and rapidity[7,8]. At national level, there are recognised methods to produce CPGs[2,9,10]. Health Technology Agencies are available worldwide to provide independent assurance and benchmarking[11,12]. Guideline developers should respond to, and guide, research. Clinicians should aim to use unbiased CPGs which take account of patient's needs with specific, unambiguous and relevant recommendations to direct management[13]. CPGs developed by global experts and aimed at international audiences should be evidence-based, rigorous in methodology

and provide a means of improving healthcare quality, although application might vary by country context.

Gender minority/trans people and healthcare

'Trans' is an umbrella term for individuals whose inner sense of self (gender identity) or how they present themselves using visual or behavioural cues (gender expression) differs from the expected stereotypes culturally assigned to their biological sex (gender)[14,15]. Gender minority is an often-used alternative population description. Like all individuals, gender minority/trans people require high-quality evidence-based healthcare[16,17], which addresses both their general and more specific needs. Gender dysphoria is a condition describing the psychological distress arising from marked incongruence between biological sex and gender identity. Until recently, an ICD-10 diagnosis of gender dysphoria was required in order to access medical transition[18], now changed to gender incongruence with ICD-11[19]. Psychological, social, mechanical, pharmaceutical or surgical interventions are offered to alleviate dysphoria, including a variety, or combinations, of reversible, partially reversible and irreversible steps[20]. These include puberty blockers, long-term sex hormone controlling medications, voice training and surgical alterations of the chest/breasts, genitalia or face, amongst others[21]. Gender dysphoria can affect many areas of life, including personal development, self-esteem, body image, employment and relationships[22]. Patient numbers referred to UK gender identity clinics for treatment of gender dysphoria and length of waiting lists have increased in the last decade[23], particularly for adolescents[24], a phenomenon also seen elsewhere[25]. Gender minority/trans people may have continuing, sometimes complex,

life-long healthcare needs whether they undergo medical transition or not. Despite efforts to depathologise, some evidence suggests unique biological, behavioural and social factors lead to health risks in gender minority/trans populations[16]. Gender minority/trans people may experience more mental health issues such as mood and anxiety disorders[26], substance use[22,23], and higher rates of suicidal ideation[24,25]. They may seek assistance with sexual health, mental health[30], substance use disorders[31], prevention and/or management of HIV[32] as well as usual general health enquiries. However, they may encounter difficulties in accessing healthcare[17], report negative healthcare experiences[33] and face discrimination and stigma[30,31].

International CPGs in gender minority/trans health and their evaluation

The reported poor population health and difficulties with accessing appropriate healthcare for gender minority/trans people suggest a need for high-quality guidance. Published CPGs for healthcare practitioners treating gender minority/trans people should guide best practice on the basis of collating the best available evidence using the best methods. Globally, there are continuing debates about ethics, law, policy and healthcare management[36]. CPGs play a role in influencing the discourse[37]. Presently, the World Professional Association for Transgender Health's (WPATH) Standards of Care Version 7 (SOCv7)[20] represent international normative standards for clinical care, thus acting as the benchmark in this field[21], despite some expressed reservations[37]. Various instruments have been developed to assess CPGs[3]. The Appraisal of Guidelines for Research and Evaluation (AGREE II instrument)[38,39] is the most comprehensively validated and evaluated tool available[3,40], employed internationally for assessing

guidelines, and was designed for use by non-expert stakeholders[39] such as healthcare providers, practicing clinicians and educators[41].

Research aim/ question

This study aimed to identify and critically appraise all published international CPGs for the assessment and care of gender minority/trans people using the AGREE II instrument.

Methods

This systematic review was conducted according to a pre-specified PROSPERO protocol (CRD42019154361) uploaded 19th December 2019. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=154361.

Inclusion and exclusion criteria

We defined CPGs as a systematically developed set of recommendations that assist practitioners and patients in the provision of healthcare in specific circumstances, produced after review and assessment of available clinical evidence[2,42–44]. CPGs published after 1st January 2010 were eligible if they (or part thereof) specifically targeted patients/population with gender minority/trans status and/or gender dysphoria, were evidence-based, with some documentation of development methodology, had international scope (more than one country, defined as a Member State of the United Nations), and were an original source. CPGs were eligible if they met the following inclusion criteria: participants/population was adults and/or children who are gender minority/trans-identifying with no exclusion due to comorbidities or age although differences/disorders in sexual development (intersex) were excluded;

exposure/intervention was any health intervention related to gender dysphoria or gender affirmation, or health concerns of gender minority/trans people, including screening, assessment, referral, diagnosis and interventions. Broad criteria were used because terminology has been in flux with changes made in both ICD and DSM diagnostic criteria[14]. There were no restrictions on setting or language. Exclusion criteria were: published before January 2010, single author, single country, adaptations of another CPG, original research, reviews, letters, opinions, editorials, case-reports, books, and commentaries.

Search strategy and guideline selection

Searches were conducted to 11th June 2020 (CM). Search terms and appropriate synonyms (as MeSH terms and text words) were developed based on population and exposures (Web/Supplementary Table 1). Six databases (platforms) were searched (EMBASE, MEDLINE, Web of Science, PsycINFO, CINAHL, Google). Six CPG websites were searched (Agency for Healthcare Research and Quality National Guideline Clearinghouse, eGuidelines and Guidelines, National Institute for Health and Care Excellence National Library for Health, Scottish Intercollegiate Guidelines Network, EBSCO DynaMed Plus, Guidelines International Network Library) and the World Health Organisation (WHO). Four specialty journals were hand-searched (International Journal of Transgender Health, Transgender Health, LGBT Health, Journal of Homosexuality) by individual reviewers (IA, DC, MJ). Four separate Google searches were performed independently by two reviewers (IA, SD) using one generic (clinical practice guidelines) plus one specific term (transgender, gender dysphoria, trans health, or gender minority) and examining the first 100 hits. International key opinion leaders (n=24) were also

approached to identify further guidelines. Reference lists of relevant reviews and all full-text studies were hand searched to identify any relevant papers or CPGs not found by database searching. All titles and abstracts were read and assessed for inclusion independently by two reviewers (SB, SD). If there was uncertainty or disagreement, or reasonable suspicion that the full-text might lead to another relevant CPG, the full-text was obtained. Google-translate was used for non-English abstracts but if a possible CPG could not be reliably excluded, the full-text paper was obtained and translated. Where full-text publications could not be accessed, authors were contacted directly. Full-text assessment to determine inclusion or exclusion from the systematic review was carried out independently by two reviewers (SB and either DC/MJ) based on the above criteria. Reasons for excluding full-texts were noted. The whole team discussed uncertainties and disagreements to achieve consensus, with voting and final adjudication by the senior author (CM).

Data extraction and quality assessment

The rationale was to identify the key international CPGs available to healthcare practitioners in this emerging, complex field of clinical practice. AGREE II[41] was considered the most appropriate tool, partly as it is validated, available and designed for any clinician to use, and benefits from several people applying the criteria independently. All authors completed AGREE II video training, a practice assessment, and two pilots whose results were discussed. Quality scoring was completed independently and anonymously by the six reviewers using the standard proforma (myAgree Plus platform, AGREE Enterprise website)[41]. AGREE II synthesis calculates quality scores from 23 appraisal criteria organised into six key domains (scope and purpose, stakeholder

involvement, rigour of development, clarity of presentation, applicability, editorial independence) and an overall assessment (Recommend for use? Options; yes, no, yes if modified). Formal descriptive data collection of included CPGs was performed independently by two authors (SB, SD). All ambiguities or discrepancies were referred to the team for discussion and to re-examine original texts and extract data. Information collected was title, author, year of publication, number of countries covered, originating organisation, audience, methods used, page and reference numbers (excluding accompanying materials), and funding. In addition, data was extracted about publication outlet (journal/website), recommendation text, and whether the quantity of information pertaining to the health of gender minority/trans people was whole, partial or minimal. All text mentions of mortality or any measures of quality of life were searched for, and noted if accompanied by a citation.

Patient and Public Involvement

An AGREE II domain prioritisation exercise was conducted in January 2020 via email, with one reminder. The UK was chosen to ensure comprehensive representation of stakeholders most relevant to the NHS. Fifty-two UK service-user stakeholder groups and gender minority/trans advocacy organisations were identified and informed about the study, with a link to the protocol. They were invited to participate in a stakeholder prioritisation of the six AGREE II domains, created using SurveyMonkey® https://www.surveymonkey.co.uk/r/WLZ55NQ and with an option to remain anonymous. The reviewer team also performed this exercise.

Outcomes

The primary outcome was the number of international CPGs addressing the health of gender minority/trans people. Secondary outcomes were: CPG quality assessment scores using AGREE II; the presence or absence of information on estimated changes in mortality or quality of life (any measure) following any specific recommended intervention, over any time interval; the consistency (or lack thereof) of recommendations across the CPGs; and the presence or absence of key messages for patients.

Strategy for Data and Statistical Analyses

Simple frequencies were used to present the stakeholder and reviewer priorities and outcomes. Following team discussion of the prioritisation exercise, no pre-specified quality threshold score was used to define high or low quality, although colour was superimposed (30% and 70%) on the final scores table to aid visual comparisons and interpretation.

Results

Figure 1 (PRISMA flow chart[45]) shows that 1,781 citations were identified, of which 134 full-text publications were read (all available, three supplied by authors) and 122 excluded (Supplementary Table W3 with reasons). Results of the domain prioritisation by stakeholders (n=19 replies, response rate 39% excluding 3 'undeliverable') and reviewers (n=6) showed that stakeholders prioritised stakeholder involvement, whereas the research team prioritised methodological rigour (Supplementary Table W2).

Primary outcome

Clinical Practice Guidelines and characteristics

Twelve CPGs (Table 1) originated from: the WHO, (n=3)[46–48], WPATH (n=2)[20,49], professional specialist/special-interest societies (n=4)[50–53], small groups of experts (n=2)[54,55] and one consortium[56]. All were published in English, in journals[49–55], the organisation's website[46–48,56], or both[20]. Guideline development methodology was variable, including use of systematic reviews (Table 1). Ten CPGs had no external review, and eight had no update plans. Transgender health recommendations made up whole (n=5)[20,49,51,53,55], partial (n=4)[46–48,54] or minimal (n=3)[50,52,56] content. The CPGs contained 10-155 pages and 20-505 references. Funding sources were wide-ranging and sometimes multiple; from government agencies, professional societies, charities and private donations. Two provided no funding details[50,54].

Secondary outcomes

Quality prioritisation and assessment

Table 2 shows that AGREE II scores were highly variable by domain (8-94%), and overall (11-94%). The two prioritised domain scores were usually comparable with the overall AGREE II quality assessment (ranges; stakeholder involvement 14-93%, methodological rigour 17-87%). Four CPGs obtained a majority opinion of 'recommend for use'[46–48,56], five CPGs had unanimous 'do not recommend'[20,49,53–55], and three had minority support with division about the extent of 'yes, if modified' [50–52](Table 2). There was wide variation in overall scores; HIV and blood-borne infection guidelines[46–48,52,56] were stronger and the quality of transition-related CPGs was poorer[20,51,53–55].

Content

Four CPGs concerning HIV prevention, transmission and care[46–48,52], and one public health guideline on population screening for blood-borne viruses[56], contained recommendations for gender minority/trans people as a 'key population'. Three CPGs were devoted to overall transition care for all gender minority/trans people[20,51,53], two to an aspect of transition[49,54], and one to transition in a specific group[55]. One oncology communication guideline contained a single recommendation relating to trans people[50]. No international guidelines were found that addressed primary care, psychological support/mental health interventions, or general medical/chronic disease care (such as cardiovascular, cancer or elderly care). The transition-related CPGs lacked methodological rigour and relied on patchier, lower-quality primary research.

Mortality and Quality of Life

Six CPGs referred to mortality[20,46,48,51,52,56] and eight to quality of life[20,46,47,49,51–53,56] (Table 2). More robust evidence with references was linked to the recommendations in the HIV and blood-borne virus CPGs. Transition CPGs had little, inconsistent data and poorer linking to evidence.

Consistency of recommendations across the CPGs

There was little overlap of topic content across the CPGs. Many recommendations were similar, but not identical, in WHO 2011[46] and 2016[48], the former not being stood down after the latter was published. Additionally, it proved impossible for all six authors independently attempting data extraction to clearly distinguish key recommendations in WPATH SOCv7[20]. After discussion, it was decided not to revisit inclusions post hoc but to abandon this protocol aim.

Patient facing material

No patient-facing material was found in any guideline.

Discussion

Statement of principal findings

A small number of international guidelines regarding gender minority/trans people's healthcare exist. Nearly half focus on HIV and other blood-borne infections and are higher-quality[46–48,52,56]. Half focus on transition and are lower-quality[20,49,51,53–55]. There is an absence of guidelines relating to primary care, mental health or longer-term medical issues. It was impossible to reliably discern key recommendations in WPATH SOCv7[20]. All CPGs lacked detail on gender minority/trans people's overall health with meagre, conflicting information regarding mortality and quality of life, and no patient-facing messages.

Strengths and weaknesses of this study

Strengths include protocol preregistration, stakeholder involvement, piloting all stages, an extensive systematic search without language restriction for any relevant current guidelines, wide inclusion criteria including grey literature, use of key opinion leaders and snowballing, double full text reading and data entry, and careful presentation of results. Using six trained reviewers, exceeding AGREE II recommendations, compensated for expected variation in scoring. Extensive searches should have mitigated loss of CPGs due to changes in terminology and diagnostic criteria. Limitations include the UK-specific stakeholder prioritisation exercise, because of particular interest in implications for the NHS; stakeholders from other countries might have different priorities. One CPG was excluded post-scoring as it was withdrawn[57]. It was arguable

if four included CPGs did meet criteria: one had not been withdrawn[46]; one contained minimal relevant content[50]; one might not have been intended as a CPG[20] (WPATH SoCv7's stated overall goal is "to provide clinical guidance for health professionals"[20], although there is no list of key recommendations nor auditable quality standards, yet it is widely used to compare procedures covered by US providers[58–60]); one variously described itself as 'position statement' and 'position study' (stating it did "not aim to provide detailed clinical guidelines for professionals such as… [named][20,51]", but evidence was obviously linked to key recommendations for clinicians[53]). Excluding these would not change overall findings or interpretation.

Comparison with other studies, discussing important differences in results

This is the first systematic review using a validated quality appraisal instrument of international CPGs addressing gender minority/trans health. It may act as a benchmark to monitor and improve population healthcare. CPG quality results correspond with, and quantitatively confirm, previously noted concerns about the evidence-base[37,61,62] and variable use of quality assessment in systematic reviews[63–65]. Previous observations have been made regarding unknown or unclear longitudinal outcomes, especially for interventions at younger ages[24]. AGREE II has been applied to CPGs in other medical fields, including cancer[66–68], diabetes[69,70], pregnancy[71,72] and depression[73]. These exercises tend to show room for improvement. Clinicians have been criticised for not using methodological rigour when writing reliable evidence-based guidelines[74], as well as not implementing high-quality CPGs[75]. Thus, finding poor quality CPGs is not confined to this area of healthcare[76]. Improvement messages are generalisable to other specialties. Although commonly found, it is not considered best practice for specialist

groups, with competing interests, to produce guidelines without external help and quality assessment[77,78].

Meaning of the study: possible explanations and implications for clinicians and policymakers

Clinicians need to be aware that the evidence-base outside HIV-related gender minority/trans health CPGs is weak and should proceed with caution. The lack of patient-facing material must be addressed, especially as medical and non-medical online material contains jargon, is unreliable and potentially misleading[79]. Policy makers need to be aware of the limited evidence-base, variations in methodological rigour, and lack of stakeholder involvement. There are implications for education and curricular content, such as that underpinning new gender identity healthcare credentials[80], which should be carefully scrutinised. The particular focus on trans people in the HIV epidemic may relate to applying public health and human rights lenses[81,82]. HIV and medical transition are only two parts of overall healthcare needs, and consideration of other aspects of gender minority/trans people's wellbeing is required. WPATH SOCv7[20] cannot be considered the current 'gold standard'. The document is due for updating and this study should be used positively to accelerate improvement. Countries might reconsider the wisdom of adapting low-quality 'off the shelf' international CPGs[83–85]. Policymakers need to invest in both primary research and high-quality systematic reviews in areas relevant for CPG and service development. Although editorial independence was the lowest priority for stakeholders, independent external review is important to avoid biases and bad practices, examine use of resources, resist commercial interests, and gain

widespread credibility outside the field. Clinicians need to explain uncertainties to patients, recruit to research and further develop a learning culture beyond empiricism.

Unanswered questions and future research

This study should be replicated as new iterations of international CPGs become available and applied to national guidelines. When the 'best available evidence' is poor, quality improvement can be driven both from inside and outside the field. Qualities required are recognition of uncertainties, less stigma, better patient and public involvement, independence and methodological rigour. The UK is fortunate in being familiar with developing priority-setting partnerships (e.g. James Lind Initiative[86]) and generating suites of clinical questions that might cover all steps in patient pathways (e.g. in partnership with Cochrane Collaboration[87]). These could underpin multidisciplinary and funded research priorities whose results feed into future better evidence-based CPGs (e.g. using SIGN[10], NICE[9] or MAGICApp[88]). The WHO demonstrates how guideline development can achieve high quality. NICE[89] has an accreditation system for UK specialist societies such as the British Association of Gender Identity Specialists[90] to raise standards and improve patient care. International guideline developers for this population need more primary research, and impetus from clinicians and scientists to build a better evidence base, especially regarding chronic diseases, minority stress[91], health behaviours, substance use, screening[65] and how interventions (e.g. hormones) might impact on long-term health (e.g. risk of cardiovascular and thromboembolic disease). Mortality and quality of life data is vital to address questions of clinical and cost-effectiveness. Sizes of benefits and harms are needed to populate patient-facing decision aids, e.g. Fact Boxes and icon arrays[92,93].

Future guidelines need more robust data from randomised controlled trials and long-term observational cohort studies, alongside development of personalised 'expected test result ranges' and interpretations pertaining to age and medical interventions such as exogenous hormonal control.

Conclusion

Gender minority/trans people deserve high-quality, holistic healthcare that is reflected in international CPGs. This vulnerable population is inadequately served by current international guidelines, limited to HIV or transition-related interventions.

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International Clinical Practice Guidelines for Gender Minority/Trans People: Systematic Review and Quality Assessment

Tables and figures list

Figure 1 – PRISMA flow diagram

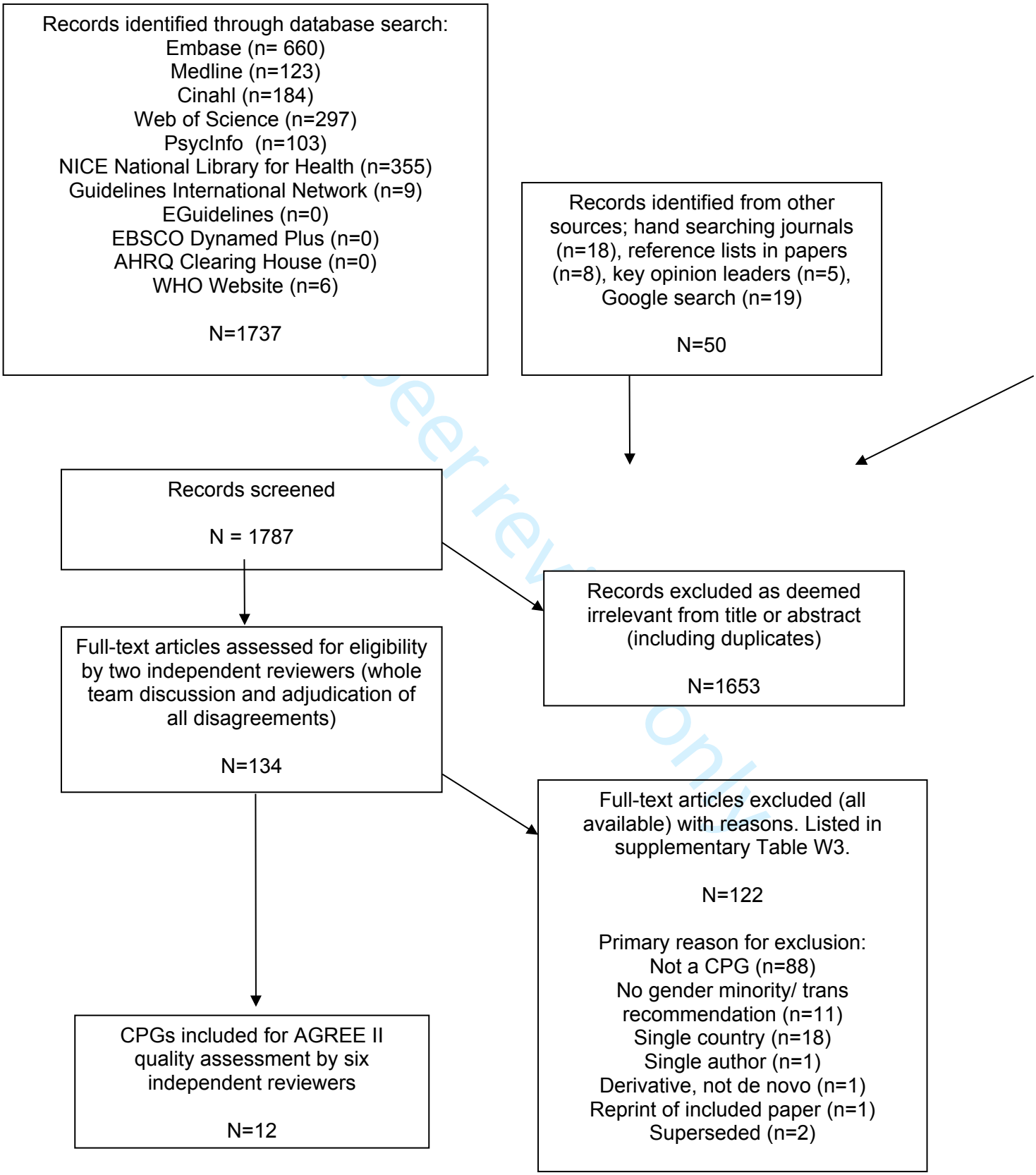

Table 1. General characteristics of included Clinical Practice Guidelines (n = 12) (Primary outcome)

Number	Author (year)	Full title	Countries covered	Origin	Primary Audience	Design (systematic review, SR, used and methods thereafter)	Planned update given	Funding
1	Coleman et al. (2012)	Standards of care for the health of transsexual, transgender, and gender nonconforming people v7	Global	WPATH	Health professionals	Work groups submit manuscripts based on prior literature reviews, no explicit links of recommendations to evidence, expert consensus. No independent external review	No	Tawani Foundation and gift from anonymous donor
2	Davies et al. (2015)	Voice and communication change for gender nonconforming individuals: giving voice to the person inside	Global	WPATH	Speech-language therapists	Review of evidence. Expert consensus. No independent external review	No	Transgender Health Information Program of British Columbia Canada
3	ECDC (2018)	Public health guidance on HIV, hepatitis B and C testing in the EU/EEA	EU/ EEA	ECDC consortium CHIP, PHE, SSAT and EATG	Member States' Public Health Professionals who coordinate the development of national guidelines or programmes for HBV, HCV and HIV testing	4 SRs, SIGN, NICE and AXIS checklists. Ad hoc internal and external expert panel, independent chair, expert consensus. No independent external review	No	Commissioned by ECDC, contractor Rigshopitalet CHIP
4	Gilligan et al. (2017)	Patient-clinician communication: American Society of Clinical Oncology consensus guideline	USA and others	ASCO	Clinicians who care for adults with cancer	9 questions (1 SR), expert consensus and a Delphi exercise. No independent external review	Regular review 3 yr check	None declared
5	Hembree et al. (2017)	Endocrine treatment of gender-dysphoric/ gender-incongruent persons: An Endocrine Society clinical practice guideline	Global	Endocrine Society	Endocrinologists, trained mental health professionals and trained physicians	2 SRs and GRADE, rest expert consensus. No independent external review	No	Endocrine Society
6	IAPHCCO (2015)	IAPAC Guidelines for optimizing the HIV care continuum for adults and adolescents	Global	IAPAC	Care providers, program managers, policymakers, affected communities, organizations, and health systems involved with implementing HIV programs and/or delivering HIV care	A systematic search of CDC database, expert consensus. No independent external review	No	IAPAC, US NIH and Office of AIDS Research
7	Ralph et al. (2010)	Trauma, gender reassignment and penile augmentation	Not specified (international publication)	Author group	Not stated (urological surgeons)	No SR. Unclear if literature review. Leading experts' consensus opinion. No independent external review	No	None declared

	Strang et al. (2016)	Initial clinical guidelines for co-occurring autism spectrum disorder and gender dysphoria or incongruence in adolescents	Not specified (international publication)	Author group	Clinicians	No SR or literature review. 2-stage Delphi consensus. No independent external review	No	Isadore and Bertha Gudelsky Family Foundation
	T'SJoen	ESSM Position Statement "Assessment and hormonal management in adolescent and adult trans people, with attention for sexual function and satisfaction"	Europe	ESSM	European clinicians working in transgender health, sexologists and other health-care professionals	No SR. Leading experts' consensus opinion. No independent external review	No	ESSM
	WHO (2011)	Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people. Recommendations for a public health approach	Global	WHO	National public health officials and managers of HIV/AIDS and STI programmes, NGOs inc. community and civil society organizations, and health workers	13 SRs for PICOs and GRADE, external GDG, and independent external review	Yes in 2015	BMZ & PEPFAR through CDC & USAID
	WHO (2012)	Guidance on oral pre-exposure prophylaxis for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV. Recommendations for use in the context of demonstration projects	Global	WHO	Countries/ Member States	4 SRs (inc values and preferences reviews) and GRADE, external GDG, and independent external review group	Yes in 2015	Bill and Melinda Gates Foundation
	WHO (2016)	Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. 2016 update	Global	WHO	National HIV programme managers and other decision-makers within ministries of health and those responsible for health policies, programmes and services in prisons.	2 new SRs in revised guidance, GRADE, external GDGs, and 79 independent external peer reviewers	Regular updates; no detail	UNAIDS, PEPFAR, Global Fund

Key: AACE, American Association of Clinical Endocrinologists; ASA, American Society of Andrology; ASCO, American Society of Clinical Oncology; ASD, autism spectrum disorder; AXIS, Appraisal Tool for Cross-Sectional Studies; BMZ, German Federal Ministry for Economic Cooperation and Development; CDC, the Centers for Disease Control and Prevention; CHIP, CHIP/Region H, Rigshospitalet, University of Copenhagen; CPG, clinical practice guideline; EATG, European Aids Treatment Group; EAU, European Association of Urology; ECDC, European Centre for Disease Prevention and Control; ESE, European Society of Endocrinology; ESPE, European Society for Pediatric Endocrinology; ESSM, European Society for Sexual Medicine EU/EEA, European Union/ European Economic Area; Global Fund, Global Fund to Fight AIDS, Tuberculosis and Malaria; GDG, guideline development group; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IAPAC, International Association of Providers of AIDS Care; IAPHCCO, International advisory panel on HIV care continuum optimization; NGO non governmental organisations; NICE, National Institute of Health and Care Excellence; NIH, National Institutes of Health; PEPFAR, US President's Emergency Plan for AIDS Relief; PES Pediatric Endocrine Society; PHE, Public Health England; SIGN, Scottish Intercollegiate Guidelines Network; SR, systematic review; SSAT, St Stephen's AIDS Trust; UNAIDS, The Unified Budget, Results and Accountability Framework of the Joint United Nations Programme on HIV/AIDS; USA, United States of America; USAID, US Agency for International Development; WHO, World Health Association; WPATH, World Professional Association for Transgender Health.

Table 2. AGREE II domain percentages and overall assessment of included guidelines, mortality/QOL measures, and existence of patient facing messages (n = 12) (secondary outcomes)

Number	Author (year)	Scope and purpose	Stakeholder Involvement	Rigour of development	Clarity and presentation	Applicability	Editorial independence	Overall Assessment	Recommendation to use	Mortality	Quality of Life	Mortality (any comment) and Quality of Life (any formal measure)
1	Coleman et al. (2012)	63%	47%	20%	37%	16%	15%	31%	Yes **0** No **5** If modified **1**	Y	Y	M: Higher in post SRS vs matched no SRS, and both pre and post SRS vs. gen popn. QoL: FtM < gen popn, FtM post breast/chest surgery > not surgery, mixed results at 15 yrs.
2	Davies et al. (2015)	62%	38%	17%	61%	28%	14%	28%	Yes **0** No **3** If modified **3**	N	Y	QoL: A voice-related TG QoL measure correlated with own and others' perception.
3	ECDC (2018)	94%	56%	55%	76%	68%	38%	69%	Yes **4** No **0** If modified **2**	Y	Y	M: Reduced by early diagnosis. QoL: Cost/QALY in anti-HCV birth cohort screening is acceptable. Universal offer HIV testing in hospital settings is highly cost effective.
4	Gilligan et al. (2017)	84%	67%	66%	81%	47%	61%	78%	Yes **2** No **0** If modified **4**	N	N	
5	Hembree et al. (2017)	65%	40%	41%	73%	29%	65%	56%	Yes **1** No **2** If modified **3**	Y	Y	M: TW/TM's CV mortality same ("insufficient very low quality data" for TM) and younger age at death after SRS. QoL: long term psychological and psychiatric issues post SRS.
6	IAPHCCO (2015)	85%	56%	61%	87%	40%	63%	81%	Yes **3** No **0** If modified **3**	Y	Y	M: Lower if early ART, easy access, immediate ART, and community distribution. QoL: ART preserves QoL, and stigma and mental health impact on QoL.
7	Ralph et al. (2010)	45%	14%	19%	64%	5%	32%	28%	Yes **0** No **5** If modified **1**	N	N	
8	Strang et al. (2016)	57%	33%	19%	39%	8%	25%	11%	Yes **0** No **6** If modified **0**	N	N	
9	T'Sjoen et al. (2020)	59%	37%	35%	58%	15%	33%	42%	Yes **0** No 4 If modified 2	N	Y	QoL: Sexual life improves after GAMI, but not to cisgender levels.
10	WHO (2011)	94%	89%	87%	86%	64%	82%	83%	Yes **5** No **0** If modified **1**	Y	Y	M: Looked for mortality evidence but none found. QoL: Positive QALYs if HIV averted.
11	WHO (2012)	85%	60%	81%	76%	41%	72%	72%	Yes **4** No **0** If modified **2**	N	Y	QoL: Positive QALYs modelled if PrEP.
12	WHO (2016)	94%	93%	81%	89%	84%	65%	94%	Yes **5** No **0** If modified **1**	Y	N	M: Lower if access and adhere to OST and at prison release, if early ART and complete TB Rx, HBV/ HCV managed; and access to post abortion care. Worse if food insecure, poor nutrition, low BMI.

Key: ART, antiretroviral therapy; CV, cardiovascular; ECDC, European Centre for Disease Prevention and Control; FtM, female-to-male; gen popn, general population; GAMI, gender affirming medical intervention; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immuno-deficiency virus; IAPHCCO, International advisory panel on HIV care continuum optimization; M, mortality; OST, opiate substitute therapy; PrEP, pre-exposure prophylaxis; QALY, quality adjusted life year; QOL, Quality of life; Rx, treatment; SR, systematic review; SRS, sex reassignment surgery; TB, tuberculosis; TG, transgender; TM, trans man; TW, trans woman; WHO, World Health Association. Two prioritised domains for **stakeholders** and **research team**. Colours to aid interpretation (not thresholds) <30 RED, 30-70 AMBER, >70 GREEN

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Supplementary/ Web/ Appendices

W1. Search terms used and search strategy for at least one database

W2. Stakeholder and review team priority scoring exercise

W3. Full text excluded studies with reasons for exclusion

W1: Literature searching – Databases searched and search terms used

Embase <1974 to 2019 July 29>

1 transgender.mp. or transgender/ (7297)
2 transsexual.mp. (2070)
3 gender identity/ or gender non-conforming.mp. (15929)
4 non-binary.mp. (219)
5 gender minority.mp. or "sexual and gender minority"/ (1582)
6 transman.mp. (20)
7 transwoman.mp. (25)
8 gender dysphoria.mp. or gender dysphoria/ (1887)
9 gender diversity.mp. (257)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (24836)
11 practice guideline/ or clinical guideline.mp. (387400)
12 10 and 11 (511)
13 limit 12 to yr="2008 - 2020" (460)

Ovid MEDLINE(R) ALL <1946 to July 29, 2019>

1 gender diversity.mp. (225)
2 gender dysphoria.mp. or Transsexualism/ or Gender Dysphoria/ or Gender Identity/ (20817)
3 gender minority.mp. or "Sexual and Gender Minorities"/ (2406)
4 Transgender Persons/ or gender non-conforming.mp. (2429)
5 non-binary.mp. (164)
6 transgender.mp. (5364)
7 transman.mp. (8)
8 transwoman.mp. (13)
9 Transsexualism/ or transsexual.mp. (3855)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (26619)
11 Practice Guidelines as Topic/ or clinical guideline.mp. (112006)
12 10 and 11 (103)

Web of Science

Search terms: (TOPIC: (((((transgender OR gender dysphoria) OR transsexual) OR gender identity) OR transman) OR transwomen) AND TOPIC: (clinical guideline OR practice guideline)) [271 results]

(TOPIC: (gender incongruence) AND TOPIC: (clinical guideline OR practice guideline))

NICE Evidence

Search terms: Transgender, gender dysphoria

CINAHL
(transgender or transsexual or transsexual or gender variant or gender non-conforming or transmen or transwomen or gender dysphoria or gender identity) AND (clinical guideline or practice guideline)

PSYCInfo
(transgender or transsexual or transexual or gender variant or gender non-conforming or transmen or transwomen or gender dysphoria or gender identity) AND (clinical guideline or practice guideline)

AHRQ National Guidelines Clearing House,
Search terms: trans, gender identity. Was stopped in 2018 – no update searches available

eGuidelines
Search terms: trans, gender identity

Guidelines International Network:
Search terms: Transgender, gender dysphoria, gender identity

WHO website – not searchable so used Google instead

Google Search terms: WHO transgender guidelines - First 100 hits examined

Update: WHO transgender guidelines 2020

W2: Stakeholder prioritisation exercise and comparison with research team

Domains	Stakeholders (n=19) #						Reviewers (n=6)					
Priority	**1 highest**	**2**	**3**	**4**	**5**	**6 lowest**	**1 highest**	**2**	**3**	**4**	**5**	**6 lowest**
Scope and purpose	***	***** *	*	**	***** *		*	*	*****	**		*
Stakeholder Involvement	***** ****	*	***	**	**	*			*	*	**	*
Rigour of development	*	*	*****	*****	****	**	*****	*				
Clarity and presentation	***	***	*****	***	*	***		*		***	*	
Applicability	*	***** **	**	*****	***			*			*	***
Editorial independence	**	*	**	*		***** ***** *		**			**	*

Key: # Numbers do not all add up to 19 as one stakeholder only gave first two preferences; * stakeholder or reviewer preference vote. Green shows highest priority and red shows lowest priority

W3: Excluded full studies with reasons for exclusion

Full Citation (n=122)	Reason(s) for exclusion
Ackerley CG, Poteat T, Kelley CF. Human Immunodeficiency Virus in Transgender Persons. *Endocrinol Metab Clin North Am* 2019;**48**:453–64. doi:10.1016/j.ecl.2019.02.007	Not a CPG. Single country.
Adams N, Pearce R, Veale J, *et al.* Guidance and Ethical Considerations for Undertaking Transgender Health Research and Institutional Review Boards Adjudicating this Research. *Transgender Heal* 2017;**2**:165–75. doi:10.1089/trgh.2017.0012	Not a CPG.
ADFAM. Including diverse families: good practice guidelines. 2010. https://adfam.org.uk/files/docs/idf_toolkit.pdf	No TG specific recommendation. Single country.
Akl EA, Kennedy C, Konda K, *et al.* Using GRADE methodology for the development of public health guidelines for the prevention and treatment of HIV and other STIs among men who have sex with men and transgender people. *BMC Public Health* 2012;**12**:386. doi:10.1186/1471-2458-12-386	Not a CPG.
American College of Obstetricians and Gynecologists, Sokkary N, Gomez-Lobo V. Committee Opinion No. 685: Care for Transgender Adolescents. *Obstet Gynecol* 2017;**129**:e11–6. doi:10.1097/AOG.0000000000001861	Not a CPG. Single country.
American Psychological Assoc. Guidelines for psychological practice with transgender and gender nonconforming people. *Am Psychol* 2015;**70**:832–64. doi:10.1037/a0039906	Single country.
American Psychological Association. Multicultural guidelines: An ecological approach to context, identity, and intersectionality, 2017. *Am Psychol Assoc*: 2017.http://www.apa.org/about/policy/multicultural-guidelines.pdf	Single country.
American Society for Reproductive Medicine, American College of Obstetricians and Gynecologists. Prepregnancy counseling: Committee Opinion No. 762. *Fertil Steril* 2019;**111**:32–42. doi:10.1016/j.fertnstert.2018.12.003	Not a CPG. No TG specific recommendation. Single country.
Baggaley R, Armstrong A, Dodd Z, *et al.* Young key populations and HIV: A special emphasis and consideration in the new WHO Consolidated Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations. *J Int AIDS Soc* 2015;**18**:85–8. doi:10.7448/IAS.18.2.19438	Not a CPG.
Barrett J. Gender Dysphoria in Adults. BMJ Best Pract. 2018.https://bestpractice.bmj.com/topics/en-gb/992	Not a CPG. Single author.
Bekker L-G, Rebe K, Venter F, *et al.* Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV-1 infection. *South Afr J HIV Med* 2016;**17**. doi:10.4102/sajhivmed.v17i1.455	Single country.
Berli JU, Capitán L, Simon D, *et al.* Facial gender confirmation surgery—review of the literature and recommendations for Version 8 of the WPATH Standards of Care. *Int J Transgenderism* 2017;**18**:264–70. doi:10.1080/15532739.2017.1302862	Not a CPG.
Bhugra D, Gupta S, Schouler-Ocak M, *et al.* EPA Guidance Mental Health Care of Migrants. *Eur Psychiatry* 2014;**29**:107–15. doi:10.1016/j.eurpsy.2014.01.003	Not a CPG. No TG specific recommendation.
Bonifacio JH, Maser C, Stadelman K, *et al.* Management of gender dysphoria in adolescents in primary care. *Can Med Assoc J* 2019;**191**:E69–75. doi:10.1503/cmaj.180672	Not a CPG. Single country.
Bonnington A, Dianat S, Kerns J, *et al.* Society of Family Planning clinical recommendations: Contraceptive counseling for transgender and gender diverse people who were female sex assigned at birth. *Contraception* Published Online First: 2020. doi:10.1016/j.contraception.2020.04.001	Single country.
Boroughs MS, Bedoya CA, O'Cleirigh C, *et al.* Toward Defining, Measuring, and Evaluating LGBT Cultural Competence for Psychologists. *Clin Psychol Sci Pract* 2015;**22**:151–71. doi:10.1111/cpsp.12098	Not a CPG. Single country.

Bourjeily G, Mehta S. Gender diversity in Obstetric Medicine. *Obstet Med* 2019;**12**:55–6. doi:10.1177/1753495X19851711	Not a CPG.
Brown B, Poteat T, Marg L, *et al.* Human Papillomavirus-Related Cancer Surveillance, Prevention, and Screening among Transgender Men and Women: Neglected Populations at High Risk. *LGBT Heal* 2017;**4**:315–9. doi:10.1089/lgbt.2016.0142	Not a CPG.
Brown GR. Recommended revisions to the world professional association for transgender health's standards of care section on medical care for incarcerated persons with gender identity disorder. *Int J Transgenderism* 2009;**11**:133–9. doi:10.1080/15532730903008073	Not a CPG. Single author.
Bruessow DM, O'Connor LM, Eaman E, *et al.* Transgender Patients: Considerations for the Family Physician. *Fam Dr A J New York State Acad Fam Physicians* 2019;**7**:36–41.	Not a CPG. Single country.
Burns ZT, Bitterman DS, Liu KX, *et al.* Towards a standard of care in oncology for transgender patients. *Lancet Oncol* 2019;**20**:331–3. doi:10.1016/S1470-2045(18)30942-2	Not a CPG. Single country.
Byne W, Bradley SJ, Coleman E, *et al.* Treatment of gender identity disorder. *Am J Psychiatry* 2012;**169**:875–6. doi:10.1176/appi.ajp.2012.169.8.875	Not a CPG.
Canady V. APA practice guidelines for females focus on their strength, resilience. *Ment Heal Wkly* 2019;**29**:1–8. doi:10.1002/mhw	Not a CPG. Single Country. Single author.
Capitán L, Gutiérrez Santamaría J, Simon D, *et al.* Facial Gender Confirmation Surgery. *Plast Reconstr Surg* 2020;**145**:818e-828e. doi:10.1097/PRS.0000000000006686	Not a CPG. Single Country.
Carswell JM, Roberts SA. Induction and Maintenance of Amenorrhea in Transmasculine and Nonbinary Adolescents. *Transgender Heal* 2017;**2**:195–201. doi:10.1089/trgh.2017.0021	Not a CPG. Single country.
Chen D, Hidalgo MA, Leibowitz S, *et al.* Multidisciplinary Care for Gender-Diverse Youth: A Narrative Review and Unique Model of Gender-Affirming Care. *Transgender Heal* 2016;**1**:117–23. doi:10.1089/trgh.2016.0009	Not a CPG.
Church of England. *Valuing All God's Children: Challenging homophobic, biphobic and transphobic bullying*. 2nd ed. Church of England Education Office 2019. https://www.churchofengland.org/sites/default/files/2019-07/Valuing All God%27s Children July 2019_0.pdf	Not a CPG.
Cohen J, Lo YR, Caceres CF, *et al.* WHO guidelines for HIV/STI prevention and care among MSM and transgender people: Implications for policy and practice. *Sex Transm Infect* 2013;**89**:536–8. doi:10.1136/sextrans-2013-051121	Not a CPG.
Cohen-Kettenis PT, Klink D. Adolescents with gender dysphoria. *Best Pract Res Clin Endocrinol Metab* 2015;**29**:485–95. doi:10.1016/j.beem.2015.01.004	Not a CPG.
Colebunders B, De Cuypere G, Monstrey S. New Criteria for Sex Reassignment Surgery: WPATH Standards of Care, Version 7, Revisited. *Int J Transgenderism* 2015;**16**:222–33. doi:10.1080/15532739.2015.1081086	Not a CPG.
Coxon J, Seal L. Hormone management of trans men. *Trends Urol Men's Heal* 2018;**9**:8–12. doi:10.1002/tre.651	Not a CPG. Single country.
D'Angelo A, Panayotidis C, Amso N, *et al.* Recommendations for good practice in ultrasound: oocyte pick up†. *Hum Reprod Open* 2019;**2019**:1689–99. doi:10.1093/hropen/hoz025	Not a CPG. No TG specific recommendation.
Dahl M, Feldman JL, Goldberg J, *et al.* Endocrine Therapy for Transgender Adults in British Columbia: Suggested Guidelines Physical Aspects of Transgender Endocrine Therapy. 2015. http://www.phsa.ca/transcarebc/Documents/HealthProf/BC-Trans-Adult-Endocrine-Guidelines-2015.pdf	Single country.
Davies S. The Evidence Behind the Practice: A Review of WPATH Suggested Guidelines in Transgender Voice and Communication. *Perspect ASHA Spec Interes Groups* 2017;**2**:64–73. doi:10.1044/persp2.SIG10.64	Single author.
De Antonio IE, Gómez-Gil E. Coordination of healthcare for transsexual persons: A multidisciplinary approach. *Curr Opin Endocrinol Diabetes Obes* 2013;**20**:585–91. doi:10.1097/01.med.0000436182.42966.31	Not a CPG.

de Haan G, Santos G-M, Arayasirikul S, *et al.* Non-Prescribed Hormone Use and Barriers to Care for Transgender Women in San Francisco. *LGBT Heal* 2015;**2**:313–23. doi:10.1089/lgbt.2014.0128	Not a CPG.
de Vries ALC, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: The Dutch approach. *J Homosex* 2012;**59**:301–20. doi:10.1080/00918369.2012.653300	Not a CPG.
Dèttore D, Ristori J, Antonelli P, *et al.* Gender dysphoria in adolescents: The need for a shared assessment protocol and proposal of the AGIR protocol. *J Psychopathol* 2015;**21**:152–8.	Not a CPG.
Deutsch MB, Green J, Keatley JA, *et al.* Electronic medical records and the transgender patient: Recommendations from the world professional association for Transgender Health EMR working group. *J Am Med Informatics Assoc* 2013;**20**:700–3. doi:10.1136/amiajnl-2012-001472	Not a CPG. Single country.
Devon Partnership NHS Trust. PG12 Pharmacological Treatment of Gender Dysphoria. 2015.https://www.gires.org.uk/wp-content/uploads/2014/08/PG12-GenderDysphoria.pdf	Single country.
Etienne Tollinche L, Burrows Walters C, Radix A, *et al.* The perioperative care of the transgender patient. *Anesth Analg* 2018;**127**:359–66. doi:10.1213/ANE.0000000000003371	Not a CPG. Single country.
European Society of Human Genetics. Genetic testing in asymptomatic minors: Recommendations of the European Society of Human Genetics. *Eur J Hum Genet* 2009;**17**:720–1. doi:10.1038/ejhg.2009.26	No TG specific recommendation. Single author.
Finlayson C, Johnson EK, Chen D, *et al.* Proceedings of the Working Group Session on Fertility Preservation for Individuals with Gender and Sex Diversity. *Transgender Heal* 2016;**1**:99–107. doi:10.1089/trgh.2016.0008	Not a CPG.
Fisher CB, Fried AL, Desmond M, *et al.* Perceived barriers to HIV prevention services for transgender youth. *LGBT Heal* 2018;**5**:350–8. doi:10.1089/lgbt.2017.0098	Not a CPG.
Francis C, Grober E, Potter E, *et al.* A Simple Guide for Simple Orchiectomy in Transition-Related Surgeries. *Sex Med Rev* 2020:3–7. doi:10.1016/j.sxmr.2019.11.004	Not a CPG. Single country.
Fraser L. Psychotherapy in the world professional association for transgender health's standards of care: Background and recommendations. *Int J Transgenderism* 2009;**11**:110–26. doi:10.1080/15532730903008057	Not a CPG. Single author.
Gamble RM, Taylor SS, Huggins AD, *et al.* Trans-specific Geriatric Health Assessment (TGHA): An inclusive clinical guideline for the geriatric transgender patient in a primary care setting. *Maturitas* 2020;**132**:70–5. doi:10.1016/j.maturitas.2019.12.005	Not a CPG. Single country.
GIRES. Guidance for GPs , other clinicians and health professionals on the care of gender variant people Transgender wellbeing and healthcare. UK Dep. Heal. 2008.https://midessexccg.nhs.uk/medicines-optimisation/clinical-pathways-and-medication-guidelines/chapter-6-endocrine-system-2/1142-guidance-for-gps-and-hormone-treatment-for-gender-dysphoria-1/file	Single country.
Goeckenjan M, Glaß K, Torka S, *et al.* Indications for fertility preservation. *Gynakologische Endokrinol* 2019;:71–7. doi:10.1007/s10304-019-0241-3	Not a CPG. Single country.
Griffith C, Akers W, Dispenza F, *et al.* Standards of Care for Research with Participants Who Identify as LGBTQ+. *J LGBT Issues Couns* 2017;**11**:212–29. doi:10.1080/15538605.2017.1380549	Not a CPG. Single country
Guidance on Gender Dysphoria for Nurses. *Nurs Stand* 2013;**28**:10. doi:10.7748/ns2013.10.28.9.10.s10	Not a CPG.
Hagen DB, Galupo MP. Trans* Individuals' Experiences of Gendered Language with Health Care Providers: Recommendations for Practitioners. *Int J Transgenderism* 2014;**15**:16–34. doi:10.1080/15532739.2014.890560	Not a CPG.
Hamidi O, Davidge-Pitts CJ. Transfeminine Hormone Therapy. *Endocrinol Metab Clin North Am* 2019;**48**:341–55. doi:10.1016/j.ecl.2019.02.001	Not a CPG. Single country.
Health Policy Project, Asia Pacific Transgender Network, United Nations Development Programme. *Blueprint for the provision of comprehensive care for trans people and trans communities in Asia and the Pacific*. Washington, DC: Futures Group, Health Policy Project 2015. http://www.asia-	Not a CPG.

pacific.undp.org/content/rbap/en/home/library/democratic_governance/hiv_aids/blueprint-for-the-provision-of-comprehensive-care-for-trans-peop/	
Heidari S, Babor TF, De Castro P, *et al.* Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use. *Res Integr Peer Rev* 2016;**1**:1–9. doi:10.1186/s41073-016-0007-6	Not a CPG.
Hembree W, Cohen-Kettenis P, Gooren L, *et al.* Endocrine treatment of gender-dysphoric/ gender-incongruent persons: an endocrine society clinical practice guideline. *Endocr Pract* 2017;**23**:1437–71.	Reprint of included paper (fully cited).
Hirsch S, Pickering J, Adler R. Meeting the Needs of Trans and Gender Diverse Youth: The Varied, Ubiquitous Role of the Speech-Language Pathologist in Voice and Communication Therapy/Training. *Perspect ASHA Spec Interes Groups* 2019;**4**:111–7. doi:10.1044/2018_PERS-SIG3-2018-0016	Not a CPG. Single country.
House H, Gaines S, Hawkins LA. Sexual and Gender Minority Adolescents: Meeting the Needs of Our LGBTQ Patients and Their Families. *Clin Pediatr Emerg Med* 2019;**20**:9–16. doi:10.1016/j.cpem.2019.02.004	Not a CPG. Single country.
Hughes LD, Berzin OKG, Leung M, *et al.* Adapting Healthcare Quality Measures to Transgender Individuals. *LGBT Heal* 2017;**4**:248–51. doi:10.1089/lgbt.2017.0009	Not a CPG. Single country.
Human Rights Campaign, American Academy of Pediatrics, American College of Osteopathic Pediatricians. Supporting & Caring for Transgender Children. 2016.http://hrc.im/supportingtranschildren	Not a CPG. Single country.
IAPAC. IAPAC Protocols for the Integrated Management of HIV and Noncommunicable Diseases. *Int Assoc Provid AIDS care* Published Online First: 2018.https://www.iapac.org/files/2018/07/IAPAC-Protocols-for-the-Integrated-Management-of-HIV-and-Noncommunicable-Diseases_3.pdf	No TG specific recommendation.
IMAP. IMAP Statement on hormone therapy for transgender people. Published Online First: 2015.https://www.ippf.org/sites/default/files/ippf_imap_transgender.pdf	Not a CPG.
In Case You Haven't Heard. *Mental Health Weekly* 2015;**25**:8-8. doi:10.1002/mhw.30307	Not a CPG.
International Association for the Study of Pain. *Guide to Pain Management in Low-Resource Settings*. Seattle: : IASP 2010. https://ebooks.iasp-pain.org/guide_to_pain_management_in_low_resource_settings	Not a CPG. No TG specific recommendation.
International Association of Physicians in AIDS Care. IAPAC – Blueprint to Address the Sexual and Reproductive Health Care and STI/HIV Prevention Needs of Adolescent Girls and Young Women. Published Online First: 2011.https://www.iapac.org/guidance/recommendations/blueprint-to-address-the-sexual-and-reproductive-health-care-and-sti-hiv-prevention-needs-of-adolescent-girls-and-young-women-in-latin-america-and-the-caribbean/	No TG specific recommendation.
International Association of Providers in AIDS Care. Recommendations for the rapid expansion of HIV self-testing in Fast-Track Cities. Published Online First: 2017.http://www.iapac.org/uploads/IAPAC-ASLM-HIVST-FTC-Recommendations-012617.pdf	No TG specific recommendation.
International Planned Parenthood Federation. IPPF. Hormonal contraception: recommendations for women at high risk of HIV. Published Online First: 2017.http://www.ippf.org/sites/default/files/2017-07/ippf_technical_brief_HC_HIV_June2017.pdf	Not a CPG. No TG specific recommendation.
International Planned Parenthood Federation. Putting sexuality back into Comprehensive Sexuality Education: making the case for a rights-based, sex-positive approach. Published Online First: 2016.https://www.ippf.org/sites/default/files/2016-10/Putting Sexuality back into Comprehensive Sexuality Education_0.pdf	Not a CPG. No TG specific recommendation.
Jungwirth, A; Diemer, T; Kopa, Z; Krausz, C; Minhas, S; Tournaye H. *EAU Guidelines on Male Infertility*. European Association of Urology 2018.	Superseded by 2020 CPG with no TG recommendations
Kaltiala-Heino R, Bergman H, Työläjärvi M, *et al.* Gender dysphoria in adolescence: current perspectives. *Adolesc Health Med Ther* 2018; **9**:31–41. doi:10.2147/AHMT.S135432	Not a CPG.
Karasic DH, Fraser L. Multidisciplinary Care and the Standards of Care for Transgender and Gender	Derivative, not de novo.

Nonconforming Individuals. *Clin Plast Surg* 2018;**45**:295–9. doi:10.1016/j.cps.2018.03.016	
Kemp K, Dibley L, Chauhan U, *et al.* Second N-ECCO Consensus Statements on the European Nursing Roles in Caring for Patients with Crohn's Disease or Ulcerative Colitis. *J Crohn's Colitis* 2018;**12**:760–76. doi:10.1093/ecco-jcc/jjy020	No TG specific recommendation.
Khosla S, Davidge-Pitts C. Skeletal considerations in the medical treatment of transgender people. *Lancet Diabetes Endocrinol* 2019;**7**:893–5. doi:10.1016/S2213-8587(19)30353-5	Not a CPG.
Klein DA, Malcolm NM, Berry-Bibee EN, et al. Quality Primary Care and Family Planning Services for LGBT Clients: A Comprehensive Review of Clinical Guidelines. *LGBT Health*. 2018;**5**:153-170. Doi:10.1089/lgbt.2017.0213	Not a CPG. No TG specific recommendation. Derivative, not de novo. Single country.
Klein M, Sathasivam A, Novoa Y, *et al.* Recent Consensus Statements in Pediatric Endocrinology: A Selective Review. *Pediatr Clin North Am* 2011;**58**:1301–15. doi:10.1016/j.pcl.2011.07.014	Not CPG. Derivative not de novo. No TG specific recommendation.
LGBT Health Program. *Guidelines and Protocols for Hormone Therapy and Primary Health Care for Trans Clients*. Toronto: Sherbourne Health Centre 2015. http://sherbourne.on.ca/lgbt-health/guidelines-protocols-for-trans-care/	Single country. Single author.
MacDonald S, Smith S. Dermatologists guide to cultural competency and the LGBTIQ patient. *Australas J Dermatol* 2018;**59**:85.	Not a CPG.
Martinez C, Rikhi R, Haque T, *et al.* Gender Identity, Hormone Therapy, and Cardiovascular Disease Risk. *Curr Probl Cardiol* 2020;**45**. doi:10.1016/j.cpcardiol.2018.09.003	Not a CPG.
Meyenburg B, Korte A, Moller B, *et al.* Gender identity disorders in childhood and adolescence (F64) / Storungen der Geschlechtsidentitat im Kindes- und Jugendalter (F64). *Prax Kinderpsychol Kinderpsychiatr* 2014;**63**:542–52.	Not a CPG.
Moreno-Pérez Ó, Esteva De Antonio I. Clinical practice guidelines for assessment and treatment of transsexualism. SEEN Identity and Sexual Differentiation Group (GIDSEEN). *Endocrinol y Nutr (English Ed* 2012;**59**:367–82. doi:10.1016/j.endoen.2012.07.004	Single country. Derivative, not de novo.
NHS England. Interim Gender Dysphoria Protocol and Service Guideline 2013/14. Published Online First: 2013.https://www.gendergp.com/wp-content/uploads/2016/03/NHS-Gender-Protocol.pdf	Not a CPG. Single country.
Oliphant J, Veale J, Macdonald J, *et al.* Guidelines for Gender Affirming Healthcare for Gender Diverse and Transgender Children, Young People and Adults in Aotearoa, New Zealand. *N Z Med J* 2018;**131**:86–96.http://www.ncbi.nlm.nih.gov/pubmed/30543615	Single country.
Olson J, Schrager SM, Clark LF, *et al.* Subcutaneous Testosterone: An Effective Delivery Mechanism for Masculinizing Young Transgender Men. *LGBT Heal* 2014;**1**:165–7. doi:10.1089/lgbt.2014.0018	Not a CPG.
Pan American Health Organization [PAHO], John Snow Inc., World Professional Association for Transgender Health, *et al. Blueprint for the Provision of Comprehensive Care for Trans Persons and Their Communities in the Caribbean and Other Anglophone Countries*. Arlington VA: John Snow Inc 2014. https://www.paho.org/hq/dmdocuments/2014/2014-cha-blueprint-comprehensive-anglo-countries.pdf	Not a CPG.
Pan American Health Organization. *Blueprint for the Provision of Comprehensive Care to Gay Men and Other Men Who Have Sex with Men (MSM) in Latin America and the Caribbean*. Washington, D.C.: 2010	No TG specific recommendation.
Patel JM, Dolitsky S, Bachman GA, *et al.* Gynecologic cancer screening in the transgender male population and its current challenges. *Maturitas* 2019;**129**:40–4. doi:10.1016/j.maturitas.2019.08.009	Not a CPG. Single country.
Phillips JC, Patsdaughter CA. Toward a Healthier Tomorrow: Competent Health and HIV Care for Transgender Persons. *J Assoc Nurses AIDS Care* 2010;**21**:183–5. doi:10.1016/j.jana.2010.02.009	Not a CPG.
Potter J, Peitzmeier SM, Bernstein I, *et al.* Cervical Cancer Screening for Patients on the Female-to-Male Spectrum: a Narrative Review and Guide for Clinicians. *J Gen Intern Med* 2015;**30**:1857–64. doi:10.1007/s11606-	Not a CPG.

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Pratt-Chapman M, Potter J. Cancer Care Considerations for Sexual and Gender Minority Patients. *Oncol Issues* 2019;**34**:26–36.https://www.accc-cancer.org/docs/documents/oncology-issues/articles/nd19/nd19-cancer-care-considerations-for-sexual-and-gender-minority-patients.pdf?sfvrsn=d116445f_2	Not a CPG. Single country.
Psychological Society of South Africa. *Practice Guidelines For Psychology Professionals Working With Sexually And Gender-Diverse People*. Johannesburg: Psychological Society of South Africa 2017. https://www.psyssa.com/wp-content/uploads/2018/04/PsySSA-Diversity-Competence-Practice-Guidelines-PRINT-singlesided.pdf	Single country.
Radix A, Sevelius J, Deutsch MB. Transgender women, hormonal therapy and HIV treatment: A comprehensive review of the literature and recommendations for best practices. *J Int AIDS Soc* 2016;**19**:1–8. doi:10.7448/IAS.19.3.20810	Not a CPG.
Reilly M, Desousa V, Garza-Flores A, *et al.* Young Children With Gender Nonconforming Behaviors and Preferences. *J Dev Behav Pediatr* 2019;**40**:60–71. doi:10.1097/DBP.0000000000000612	Not a CPG. Single country.
Reisner SL, Pardo ST, Gamarel KE, *et al.* Substance use to cope with stigma in healthcare among U.S. female-to-male trans masculine adults. *LGBT Heal* 2015;**2**:324–32. doi:10.1089/lgbt.2015.0001	Not a CPG.
Safer JD, Tangpricha V. Care of Transgender persons. *N Engl J Med* 2019;**381**:2451–60. doi:10.1056/NEJMcp1903650	Not a CPG. Single country.
Salas-Humara C, Sequeira GM, Rossi W, *et al.* Gender affirming medical care of transgender youth. *Curr Probl Pediatr Adolesc Health Care* 2019;**49**:1–21. doi:10.1016/j.cppeds.2019.100683	Not a CPG. Single country.
Schechter LS, D'Arpa S, Cohen MN, *et al.* Gender Confirmation Surgery: Guiding Principles. *J Sex Med* 2017;**14**:852–6. doi:10.1016/j.jsxm.2017.04.001	Not a CPG.
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World Health Organization. *Preventing Suicide A Community Engagement Toolkit*. 2018. https://apps.who.int/iris/bitstream/handle/10665/272860/9789241513791-eng.pdf	Not a CPG. No TG specific recommendation.
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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	7-9
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	10
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	10
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	10-11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	W1 (Suppl)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	12
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	12-13
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	N/A (in AGREE)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	AGREE
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	14
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Within AGREE
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	None
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	14 & Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	15 & Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	None
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	10-11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	W1 (Suppl)
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PRISMA 2009 Checklist

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Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	14-19, Table 1, W3,W4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	19-24, Table 2
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Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	25-29
FUNDING			
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International Clinical Practice Guidelines for Gender Minority/Trans People: Systematic Review and Quality Assessment

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International Clinical Practice Guidelines for Gender Minority/Trans People: Systematic Review and Quality Assessment

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Structured abstract

Objectives: To identify and critically appraise published clinical practice guidelines (CPGs) regarding health care of gender minority/trans people.

Design: Systematic review and quality appraisal using AGREE II (Appraisal of Guidelines for Research and Evaluation tool), including stakeholder domain prioritisation.

Setting: Six databases and six CPG websites were searched, and international key opinion leaders approached.

Participants: CPGs relating to adults and/or children who are gender minority/trans with no exclusions due to comorbidities, except differences in sex development.

Intervention: Any health-related intervention connected to the care of gender minority/trans people.

Main outcome measures: Number and quality of international CPGs addressing the health of gender minority/trans people, information on estimated changes in mortality or quality of life (QoL), consistency of recommended interventions across CPGs, and appraisal of key messages for patients.

Results: Twelve international CPGs address gender minority/trans people's healthcare as complete (n=5), partial (n=4) or marginal (n=3) focus of guidance. The quality scores have a wide range and heterogeneity whichever AGREE II domain is prioritised. Five higher-quality CPGs focus on HIV and other blood-borne infections (overall assessment scores 69-94%). Six lower-quality CPGs concern transition-specific interventions (overall assessment scores 11-56%). None deal with primary care, mental health, or longer-term medical issues. Sparse information on estimated changes in mortality and QoL is

conflicting. Consistency between CPGs could not be examined due to unclear recommendations within the World Professional Association of Transgender Health Standards of Care Version 7 and a lack of overlap between other CPGs. None provide key messages for patients.

Conclusions: A paucity of high-quality guidance for gender minority/trans people exists, largely limited to HIV and transition, but not wider aspects of healthcare, mortality or QoL. Reference to AGREE II, use of systematic reviews, independent external review, stakeholder participation and patient facing material might improve future CPG quality.

Trial registration: PROSPERO (CRD42019154361)

Article summary

Strengths and limitations of this study

- First systematic review to identify and use a validated quality appraisal instrument to assess all international CPGs addressing gender minority/trans health.
- International CPGs were studied due to their influential status in gender minority/trans health, though further research is needed on national and local CPGs.
- An innovative prioritisation exercise was performed to elicit stakeholders' priorities and inform the setting of AGREE II quality thresholds, however those stakeholder priorities may not be applicable outside the UK.
- An inclusive approach using wide criteria, extensive searches and approaching key opinion leaders should have allowed the study to identify all relevant international CPGs, however it is possible some may have been missed.

Introduction

Assessing the quality of clinical practice guidelines

Evidence-based practice integrates best available research with clinical expertise and the patient's unique values and circumstances. High-quality clinical practice guidelines (CPGs) support high quality health care delivery. They can guide clinicians and policy makers to improve care, reduce variation in clinical practice, thereby affecting patient safety and outcomes. The Institute of Medicine defines CPGs as: "statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options"[1], though other definitions exist[2]. Recommendations are used alongside professional judgement, directly or within decision aids, in training and practice. CPGs are important but have limitations depending on evidence selection and development processes[3]. GRADE (Grading of Recommendations, Assessment, Development and Evaluation) was developed to address the evidence that is selected and appraised during CPG development[4–6]. Using a systematic approach and transparent framework for developing and presenting summaries of evidence, GRADE is the most widely adopted tool worldwide for grading the quality of evidence and making recommendations[7], but does not alone ensure a CPG is high quality. Strength of evidence is only one component of what makes a 'good' CPG; factors such as transparency, rigour, independence, multidisciplinary input, patient and public involvement, avoidance of commercial influences and rapidity[8,9] should be also considered. Broader domains of CPG quality are included in the Appraisal of Guidelines for Research and Evaluation instrument AGREE II[10–12]. Despite widely recognized principles and methods for developing

sound CPGs, current research shows that guidelines on various topics lack appropriate uptake of systematic review methodologies in their development[13], give recommendations that conflict with scientific evidence[14], or do not adequately take into account existing CPG quality and reporting assessment tools[15]. This emphasizes the ongoing need to appraise guidelines to ensure evidence-informed care.

Healthcare for gender minority/trans people

'Trans' is an umbrella term for individuals whose inner sense of self (gender identity) or how they present themselves using visual or behavioural cues (gender expression) differs from the expected stereotypes (gender) culturally assigned to their biological sex[16]. Gender minority is an often-used alternative population description. Some gender minority/trans people may seek medical transition, which involves interventions such as hormones or surgery that alter physical characteristics and align appearance with gender identity. Patient numbers referred to UK gender identity clinics and length of waiting lists have increased in the last decade, particularly for adolescents[17], a phenomenon seen elsewhere[18]. Gender minority/trans people may have continuing, sometimes complex, life-long healthcare needs whether they undergo medical transition or not. Gender minority/trans people may experience more mental health issues such as mood and anxiety disorders[19], substance use[20], and higher rates of suicidal ideation[21]. They may seek assistance with sexual health, mental health[22], substance use disorders[23], prevention and/or management of HIV[24] as well as usual general health enquiries. However, they may encounter difficulties in accessing healthcare[25], reporting negative healthcare experiences[26], discrimination and stigma[27,28]. Like all individuals,

gender minority/trans people require high-quality evidence-based healthcare[25,29] addressing general and specific needs.

Guidelines used internationally and in the UK

The quality of current guidelines on gender minority/trans health is unclear. The World Professional Association for Transgender Health (WPATH) Standards of Care Version 7 (SOCv7)[30] represent normative standards for clinical care, acting as a benchmark in this field[31]. Globally, many national and local guidelines[32–35] are adaptations of, acknowledge being influenced by, or are intended to complement WPATH SOCv7[30], despite expressed reservations that WPATH SOCv7[30] is based on lower-quality primary research, the opinions of experts and lacks grading of evidence[36].

In the UK, an advocacy group worked to incorporate WPATH SOCv7[30] into national practice[37]. WPATH SOCv7[30] informs National Health Service (NHS) gender identity clinics[38] and guidelines produced by the Royal College of Psychiatrists (without use of GRADE)[39]. No CPGs were available from the National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), British Association of Gender Identity Specialists, British Psychological Society or other medical Royal Colleges, although the Royal College of General Practitioners issued a position statement on gender minority/trans healthcare in 2019[40]. Assessing quality of international CPGs such as WPATH SOCv7[30] has practice implications for the NHS[38] and private sector. CPGs with international scope may present additional challenges (e.g. the implementability of key recommendations might not be easily translated among different contexts) but they seem to influence discourse around gender minority/trans health[36]. No prior study has investigated the number and quality of

guidelines to support the care and well-being of gender minority/trans people. The purpose of this research was to identify and critically appraise all published international CPGs for the healthcare of gender minority/trans people.

Methods

Approach/ Research Design

The rationale was to identify the key CPGs available to healthcare practitioners in this field of clinical practice. Following preliminary searches, we chose international CPGs in view of WPATH's influence within the UK and elsewhere, and to avoid 'double-counting'. We considered AGREE II[10–12] the most appropriate tool; it is the most comprehensively validated and evaluated instrument available for assessing CPGs[41,42], designed for use by non-expert stakeholders[10] such as healthcare providers, practicing clinicians and educators[11]. It benefits from clear instructions and prompts regarding scoring and several people applying the criteria independently (a minimum of two reviewers, but four are recommended). AGREE II synthesis calculates quality scores from 23 appraisal criteria organised into six key domains (scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, editorial independence) and an overall assessment of "Recommend for use?" (Answer options; yes, no, yes if modified). This systematic review was conducted according to a pre-specified PROSPERO protocol (CRD42019154361) https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=154361 uploaded 19th December 2019. The MEDLINE strategy was straightforward; although not formally processed[43], it was peer-reviewed by one information specialist.

Inclusion and exclusion criteria

We defined CPGs as a systematically developed set of recommendations that assist practitioners and patients in the provision of healthcare in specific circumstances, produced after review and assessment of available clinical evidence[1,2,44–46]. CPGs published after 1st January 2010 were eligible if they (or part thereof) specifically targeted patients/population with gender minority/trans status and/or gender dysphoria, were evidence-based, with some documentation of development methodology, had international scope (more than one country, defined as a Member State of the United Nations), and were an original source. We chose the timeframe to focus on the most recent guidelines, currently applicable to practice, and to include WPATH SOCv7[30]. CPGs were eligible if they met the following inclusion criteria: participants/population was adults and/or children who are gender minority/trans with no exclusion due to comorbidities or age although differences/disorders in sex development (intersex) were excluded; exposure/intervention was any health intervention related to gender dysphoria or gender affirmation, or health concerns of gender minority/trans people, including screening, assessment, referral, diagnosis and interventions. We excluded previous versions of the same CPG. We used broad criteria because terminology has been in flux with changes made in both International Classification of Diseases and Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria[16]. There were no restrictions on setting or language.

Search strategy and guideline selection

We conducted the searches up to 11th June 2020 (CM), using search terms and appropriate synonyms (as MeSH terms and text words) that we developed based on population and exposures (Web/Supplementary Table 1). We searched six databases (EMBASE, MEDLINE, Web of Science, PsycINFO, CINAHL, LILACS) and six CPG websites (Agency for Healthcare Research and Quality National Guideline Clearinghouse [NGC], eGuidelines and Guidelines, National Institute for Health and Care Excellence National Library for Health, Scottish Intercollegiate Guidelines Network, EBSCO DynaMed Plus, Guidelines International Network Library) and the World Health Organisation (WHO). The NGC closed in 2017 but CM hand-searched the archive. In addition to protocol, individual reviewers (IA, DC, MJ) hand-searched four specialty journals (International Journal of Transgender Health, Transgender Health, LGBT Health, Journal of Homosexuality) to ensure key subject-relevant sources of abstracts were thoroughly checked. In order to find potential grey literature CPGs outwith the scholarly literature, two reviewers (IA, SD) independently performed four separate Google searches (not GoogleScholar as mistated in the protocol) by using one generic (clinical practice guidelines) plus one specific term (transgender, gender dysphoria, trans health, or gender minority) and examining the first 100 hits. We identified International Key Opinion Leaders via publications known to reviewers (DC, SD) (n=24) and contacted them via one email and reminder to identify further guidelines. Reference lists of relevant reviews and all full-text studies were hand-searched to identify any relevant papers or CPGs not found by database searching. Two reviewers (SB, SD) independently read all titles and abstracts and assessed for inclusion. If there was uncertainty or disagreement, or reasonable suspicion that the full-text might lead to another relevant

CPG, the full-text was obtained. Non-English abstracts were Google-translated but if a possible CPG could not be reliably excluded, the full-text paper was obtained and translated. Where full-text publications could not be accessed, we contacted authors directly. Two reviewers (SB and either DC/MJ) independently carried out full-text assessment to determine inclusion or exclusion from the systematic review based on the above criteria, and noted reasons for excluding full-texts. The whole team discussed uncertainties and disagreements to achieve consensus, with voting and final adjudication by the senior author (CM).

Data extraction

Two reviewers (SB, SD) independently collected formal descriptive data of included CPGs. All ambiguities or discrepancies were referred to the team for discussion and to re-examine original texts and extract data. Information collected was title, author, year of publication, number of countries covered, originating organisation, audience, methods used, page and reference numbers (excluding accompanying materials), and funding. Key recommendations were extracted for comparison between CPGs. We searched for all text mentions of mortality or any measures of quality of life (QoL), and noted if accompanied by a citation. All patient facing material was extracted. In addition, we extracted data about publication outlet (journal/website), and whether the quantity of information pertaining to the health of gender minority/trans people represented a complete, partial or marginal proportion of recommendations in the CPG.

Outcomes

Outcomes were: the number and quality assessment (using AGREE II) of international CPGs addressing the health of gender minority/trans people; analysis and comparison of

the presence or absence of information on estimated changes in mortality or QoL (any measure) following any specific recommended intervention, over any time interval; the consistency (or lack thereof) of recommendations across the CPGs; and the presence (or absence) of key messages for patients.

Quality assessment

All authors completed AGREE II video training, a practice assessment, and two pilots whose results were discussed. The six reviewers (IA, SB, DC, SD, MJ, CM) independently and anonymously completed quality scoring on every CPG by rating each of the items using the standard proforma on the myAgree Plus online platform (AGREE Enterprise website)[11], which also calculated group appraisal scores.

Patient and Public Involvement

The AGREE II instrument generates quality scores but does not set specific parameters for what constitutes high quality, recommending that decisions about defining such thresholds should be made prior to performing appraisals, considering relevant stakeholders and the context in which the CPG is used[11]. To help set quality thresholds, we conducted an AGREE II domain prioritisation exercise in January 2020 via email, with one reminder. It was considered impossible to ensure comprehensive representation of international stakeholders. We chose the UK for feasibility, albeit validity might be limited to the NHS. Fifty-two UK service-user stakeholder groups and gender minority/trans advocacy organisations, identified via reviewer knowledge and internet searches (IA, SB, DC, SD, MJ, CM), were informed about the study. They were invited to participate in a stakeholder prioritisation of the AGREE II domains, created using SurveyMonkey® and with an option to remain anonymous

(https://www.surveymonkey.co.uk/r/WLZ55NQ gives invitation wording, links to resources and protocol). The reviewer team performed an anonymous prioritisation for comparison.

Strategy for Data and Statistical Analyses

Simple frequencies were used to present the stakeholder and reviewer priorities, and outcomes. Following team discussion of the prioritisation exercise results, no pre-specified quality threshold score was used to define high or low quality, although colour was superimposed (≤30%, 31-69% and ≥70%) on the final scores table to aid visual comparisons and interpretation.

Results

Search results

Figure 1 (PRISMA flow chart[47]) shows that 1,815 citations were identified, of which 134 full-text publications were read (all available, three supplied by authors) and 122 excluded (Supplementary Table W2 with reasons).

Data extraction

Table 1 shows the characteristics of the CPGs. Supplementary Tables W3 and W4 show raw data of key recommendations and mortality and QoL evidence.

Number and characteristics of Clinical Practice Guidelines

Twelve CPGs (Table 1) originated from: WHO (n=3)[48–50], WPATH (n=2)[30,51], professional specialist/special-interest societies (n=4)[52–55], small groups of experts (n=2)[56,57] and one consortium[58]. All were published in English, in journals[51–57], the organisation's website[48–50,58], or both[30]. Guideline development methodology

was variable, including use of systematic reviews (Table 1). Ten CPGs had no external review, eight had no update plans. Gender minority/trans health recommendations made up complete (n=5)[30,51,53,55,57], partial (n=4)[48–50,56] or marginal (n=3)[52,54,58] focus of content. CPGs contained 10 to 155 pages, and 20 to 505 references. Funding sources were wide-ranging and sometimes multiple, from government agencies, professional societies, charities and private donations. Two CPGs provided no funding details[52,56].

Table 1. General characteristics of included Clinical Practice Guidelines (n = 12)

Number	Author (year)	Full title	Countries covered	Origin	Primary Audience	Design (systematic review, SR, used and methods thereafter)	Planned update given	Funding
1	Coleman et al. (2012)	Standards of care for the health of transsexual, transgender, and gender nonconforming people v7	Global	WPATH	Health professionals	Work groups submit manuscripts based on prior literature reviews, no explicit links of recommendations to evidence, expert consensus. No independent external review	No	Tawani Foundation and gift from anonymous donor
2	Davies et al. (2015)	Voice and communication change for gender nonconforming individuals: giving voice to the person inside	Global	WPATH	Speech-language therapists	Review of evidence. Expert consensus. No independent external review	No	Transgender Health Information Program of British Columbia Canada
3	ECDC (2018)	Public health guidance on HIV, hepatitis B and C testing in the EU/EEA	EU/ EEA	ECDC consortium CHIP, PHE, SSAT and EATG	Member States' Public Health Professionals who coordinate the development of national guidelines or programmes for HBV, HCV and HIV testing	4 SRs, SIGN, NICE and AXIS checklists. Ad hoc internal and external expert panel, independent chair, expert consensus. No independent external review	No	Commissioned by ECDC, contractor Rigshopitalet CHIP
4	Gilligan et al. (2017)	Patient-clinician communication: American Society of Clinical Oncology consensus guideline	USA and others	ASCO	Clinicians who care for adults with cancer	9 questions (1 SR), expert consensus and a Delphi exercise. No independent external review	Regular review 3 yr check	None declared
5	Hembree et al. (2017)	Endocrine treatment of gender-dysphoric/ gender-incongruent persons: An Endocrine Society clinical practice guideline	Global	Endocrine Society	Endocrinologists, trained mental health professionals and trained physicians	2 SRs and GRADE, rest expert consensus. No independent external review	No	Endocrine Society
6	IAPHCCO (2015)	IAPAC Guidelines for optimizing the HIV care continuum for adults and adolescents	Global	IAPAC	Care providers, program managers, policymakers, affected communities, organizations, and health systems involved with	A systematic search of CDC database, expert consensus. No independent external review	No	IAPAC, US NIH and Office of AIDS Research

					implementing HIV programs and/or delivering HIV care			
7	Ralph et al. (2010)	Trauma, gender reassignment and penile augmentation	Not specified (international publication)	Author group	Not stated (urological surgeons)	No SR. Unclear if literature review. Leading experts' consensus opinion. No independent external review	No	None declared
8	Strang et al. (2016)	Initial clinical guidelines for co-occurring autism spectrum disorder and gender dysphoria or incongruence in adolescents	Not specified (international publication)	Author group	Clinicians	No SR or literature review. 2-stage Delphi consensus. No independent external review	No	Isadore and Bertha Gudelsky Family Foundation
9	T'SJoen	ESSM Position Statement "Assessment and hormonal management in adolescent and adult trans people, with attention for sexual function and satisfaction"	Europe	ESSM	European clinicians working in transgender health, sexologists and other health-care professionals	No SR. Leading experts' consensus opinion. No independent external review	No	ESSM
10	WHO (2011)	Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people. Recommendations for a public health approach	Global	WHO	National public health officials and managers of HIV/AIDS and STI programmes, NGOs inc. community and civil society organizations, and health workers	13 SRs for PICOs and GRADE, external GDG, and independent external review	Yes in 2015	BMZ & PEPFAR through CDC & USAID
11	WHO (2012)	Guidance on oral pre-exposure prophylaxis for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV. Recommendations for use in the context of demonstration projects	Global	WHO	Countries/ Member States	4 SRs (inc values and preferences reviews) and GRADE, external GDG, and independent external review group	Yes in 2015	Bill and Melinda Gates Foundation
12	WHO (2016)	Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. 2016 update	Global	WHO	National HIV programme managers and other decision-makers within ministries of health and those responsible for health policies, programmes and services in prisons.	2 new SRs in revised guidance, GRADE, external GDGs, and 79 independent external peer reviewers	Regular updates; no detail	UNAIDS, PEPFAR, Global Fund

Key: AACE, American Association of Clinical Endocrinologists; ASA, American Society of Andrology; ASCO, American Society of Clinical Oncology; ASD, autism spectrum disorder; AXIS, Appraisal Tool for Cross-Sectional Studies; BMZ, German Federal Ministry for Economic Cooperation and Development; CDC, the Centers for Disease Control and Prevention; CHIP, CHIP/Region H, Rigshospitalet, University of Copenhagen; CPG, clinical practice guideline; EATG, European Aids Treatment Group; EAU, European

Association of Urology; ECDC, European Centre for Disease Prevention and Control; ESE, European Society of Endocrinology; ESPE, European Society for Pediatric Endocrinology; ESSM, European Society for Sexual Medicine EU/EEA, European Union/ European Economic Area; Global Fund, Global Fund to Fight AIDS, Tuberculosis and Malaria; GDG, guideline development group; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IAPAC, International Association of Providers of AIDS Care; IAPHCCO, International advisory panel on HIV care continuum optimization; NGO non governmental organisations; NICE, National Institute of Health and Care Excellence; NIH, National Institutes of Health; PEPFAR, US President's Emergency Plan for AIDS Relief; PES Pediatric Endocrine Society; PHE, Public Health England; SIGN, Scottish Intercollegiate Guidelines Network; SR, systematic review; SSAT, St Stephen's AIDS Trust; UNAIDS, The Unified Budget, Results and Accountability Framework of the Joint United Nations Programme on HIV/AIDS; USA, United States of America; USAID, US Agency for International Development; WHO, World Health Association; WPATH, World Professional Association for Transgender Health.

A thirteenth CPG was excluded post-scoring as it had been superseded by a 2020 version without recommendations for gender minority/trans people[59]. It was arguable if four included CPGs did meet criteria: one had not been withdrawn[48]; one contained minimal relevant content[52]; one might not have been intended as a CPG[30] (although WPATH SOCv7's stated overall goal is "to provide clinical guidance for health professionals"[30] it contains no list of key recommendations nor auditable quality standards, yet is widely used to compare procedures covered by US providers[60,61]); one variously described itself as 'position statement' and 'position study' (stating it did "not aim to provide detailed clinical guidelines for professionals such as… [named][30,53]", but evidence was obviously linked to key recommendations for clinicians[55]). After discussion it was decided not to exclude these borderline CPGs, as the definition of CPG in the protocol was intended to favour an inclusive approach.

Quality prioritisation and assessment

Results of the domain prioritisation by stakeholders (n=19 replies, response rate 39% excluding 3 'undeliverable') and reviewers (n=6) showed that stakeholders prioritised stakeholder involvement, whereas the research team prioritised methodological rigour (Supplementary Table W5). No stakeholder asked for clarification or more information.

Table 2 shows AGREE II scores by domain (8-94%), and overall (11-94%). The quality scores have a wide range and heterogeneity. Five CPGs focused on trans people as a key population for HIV and other blood-borne infections (overall assessment scores 69-94%). Six CPGs concerned transition-specific interventions (overall assessment scores 11-56%). Transition-related CPGs tended to lack methodological rigour and rely on patchier, lower-quality primary research. The two prioritised domain scores were usually

comparable with the overall AGREE II quality assessment (ranges; stakeholder involvement 14-93%, methodological rigour 17-87%). Four CPGs obtained a majority opinion 'recommend for use'[48–50,58], five CPGs had unanimous 'do not recommend'[30,51,55–57], and three had minority support with division about the extent of 'yes, if modified' [52–54](Table 2). Despite wide variation there was a pattern; HIV and blood-borne infection guidelines[48–50,54,58] were higher quality, and those focusing on transition were lower quality[30,53,55–57].

Table 2. AGREE II domain percentages and overall assessment of included guidelines, and summary of mortality/quality of life measures (n = 12)

Number	Author (year)	Scope and purpose	Stakeholder Involvement	Rigour of development	Clarity and presentation	Applicability	Editorial independence	Overall Assessment	Recommendation to use	Mortality	Quality of Life	Mortality (any comment) and Quality of Life (any formal measure)
1	Coleman et al. (2012)	63%	47%	20%	37%	16%	15%	31%	Yes **0** No **5** If modified **1**	Y	Y	M: Higher in post SRS vs matched no SRS, and both pre and post SRS vs. gen popn. QoL: FtM < gen popn, FtM post breast/chest surgery > not surgery, mixed results at 15 yrs.
2	Davies et al. (2015)	62%	38%	17%	61%	28%	14%	28%	Yes **0** No **3** If modified **3**	N	Y	QoL: A voice-related TG QoL measure correlated with own and others' perception.
3	ECDC (2018)	94%	56%	55%	76%	68%	38%	69%	Yes **4** No **0** If modified **2**	Y	Y	M: Reduced by early diagnosis. QoL: Cost/QALY in anti-HCV birth cohort screening is acceptable. Universal offer HIV testing in hospital settings is highly cost effective.
4	Gilligan et al. (2017)	84%	67%	66%	81%	47%	61%	78%	Yes **2** No **0** If modified **4**	N	N	
5	Hembree et al. (2017)	65%	40%	41%	73%	29%	65%	56%	Yes **1** No **2** If modified **3**	Y	Y	M: TW/TM's CV mortality same ("insufficient very low quality data" for TM) and younger age at death after SRS. QoL: long term psychological and psychiatric issues post SRS.
6	IAPHCCO (2015)	85%	56%	61%	87%	40%	63%	81%	Yes **3** No **0** If modified **3**	Y	Y	M: Lower if early ART, easy access, immediate ART, and community distribution. QoL: ART preserves QoL, and stigma and mental health impact on QoL.
7	Ralph et al. (2010)	45%	14%	19%	64%	5%	32%	28%	Yes **0** No **5** If modified **1**	N	N	
8	Strang et al. (2016)	57%	33%	19%	39%	8%	25%	11%	Yes **0** No **6** If modified **0**	N	N	
9	T'Sjoen et al. (2020)	59%	37%	35%	58%	15%	33%	42%	Yes **0** No 4 If modified 2	N	Y	QoL: Sexual life improves after GAMI, but not to non-TG levels.
10	WHO (2011)	94%	89%	87%	86%	64%	82%	83%	Yes **5** No **0** If modified **1**	Y	Y	M: Looked for mortality evidence but none found. QoL: Positive QALYs if HIV averted.
11	WHO (2012)	85%	60%	81%	76%	41%	72%	72%	Yes **4** No **0** If modified **2**	N	Y	QoL: Positive QALYs modelled if PrEP.
12	WHO (2016)	94%	93%	81%	89%	84%	65%	94%	Yes **5** No **0** If modified **1**	Y	N	M: Lower if access and adhere to OST and at prison release, if early ART and complete TB Rx, HBV/ HCV managed; and access to post abortion care. Worse if food insecure, poor nutrition, low BMI.

Key: ART, antiretroviral therapy; CV, cardiovascular; ECDC, European Centre for Disease Prevention and Control; FtM, female-to-male; gen popn, general population; GAMI, gender affirming medical intervention; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immuno-deficiency virus; IAPHCCO, International advisory panel on HIV care continuum optimization; M, mortality; OST, opiate substitute therapy; PrEP, pre-exposure prophylaxis; QALY, quality adjusted life year; QoL, Quality of life; Rx, treatment; SR, systematic review; SRS, sex reassignment surgery; TB, tuberculosis; TG, trans people/gender-minority; TM, trans man; TW, trans woman; WHO, World Health Association. Two prioritised domains for **stakeholders** **and** **research team**. Colours to aid interpretation (not thresholds) ≤30 RED, 31-69 AMBER, ≥70 GREEN

Content

Four CPGs concerning HIV prevention, transmission and care[48–50,54], and one public health guideline on population screening for blood-borne viruses[58], contained recommendations for gender minority/trans people as a 'key population'. Three CPGs were devoted to overall transition care for all gender minority/trans people[30,53,55], two to an aspect of transition[51,56], and one to transition in a specific group[57]. One oncology communication guideline contained a single recommendation relating to gender minority/trans people[52]. No international guidelines were found that addressed primary care, psychological support/mental health interventions, or general medical/chronic disease care (such as cardiovascular, cancer or elderly care).

Mortality and Quality of Life

Six CPGs referred to mortality[30,48,50,53,54,58] and eight to QoL[30,48,49,51,53–55,58] (Table 2). Supplementary Table W4 shows all extractions of sentences relating to mortality or morbidity, associated references and which CPGs included no such data. More robust evidence was linked to the recommendations in the HIV and blood-borne virus CPGs whereas there was little, inconsistent data and poorer linking to evidence in transition-related CPGs.

Consistency of recommendations across the CPGs

Supplementary Table W5 contains all extracted key recommendations where these could be distinguished. It shows little overlap of topic content across the CPGs. Many recommendations in WHO 2011[48] and 2016[50] were similar, but not identical, the former not being stood down after the latter was published. No statements were highlighted by the WPATH SOCv7[30] authors as key recommendations, and it proved

impossible for all six reviewers independently performing data extraction to identify them. The total number of extracted recommendations ranged between 0 to 168 with little consistency or agreement on what passages were selected. Some extracted statements might have been intended as recommendations or standards, but many were flexible, disconnected from evidence and could not be used by individuals or services to benchmark practice. After discussion of this incoherence within WPATH SOCv7[30] and our inability therefore to compare recommendations across all CPGs, it was decided not to revisit inclusions post hoc but to abandon this protocol aim.

Patient facing material

No patient-facing material was found in any guideline.

Discussion

Statement of principal findings

Variable quality international CPGs regarding gender minority/trans people's healthcare contain little, conflicting information on mortality and QoL, no patient facing messages and inconsistent use of systematic reviews in generating recommendations. A major finding is that the scope of the guidelines is confined to HIV/STI prevention or management of transition with an absence of guidelines relating to other medical issues. WPATH SOCv7[30] cannot be considered 'gold standard'.

Strengths and weaknesses of this study

Strengths include protocol preregistration, stakeholder involvement, piloting all stages, an extensive systematic search without language restriction for any relevant current guidelines, wide inclusion criteria including grey literature, use of key opinion leaders,

close attention to avoidance of bias, double full-text reading and data entry, and careful presentation of results. Six trained reviewers, exceeding AGREE II recommendations[11], compensated for expected variation in scoring. Extensive searches should have mitigated loss of CPGs. Limitations include some uncertainty about stakeholder understanding despite a good response rate, and generalisability of the prioritisation only to the UK; stakeholders elsewhere might have different priorities. Focusing only on international CPGs might have missed higher quality national and local CPGs derived from them or written de novo. The social acceptance and consequent healthcare system coverage of gender minority/trans health related interventions vary among different countries, which may limit the space for international and multinational guidelines. While the search strategy yielded an oncology communication CPG with a single recommendation for gender minority/trans people[52], other general health CPGs with similar solo statements might have been missed.

Comparison with other studies, discussing important differences in results

This is the first systematic review using a validated quality appraisal instrument of international CPGs addressing gender minority/trans health. It may act as a benchmark to monitor and improve population healthcare. CPG quality results correspond with, and quantitatively confirm, previously noted concerns about the evidence-base[36,62,63] and variable use of quality assessment in systematic reviews[64–66], in a healthcare field with unknown or unclear longitudinal outcomes[17]. AGREE II has been applied to CPGs in other medical areas, including cancer[67], diabetes[68], pregnancy[69] and depression[70]. These exercises tend to show room for improvement. Developers have been criticised for not using methodological rigour when writing reliable evidence-based

guidelines[71], as well as not implementing high-quality CPGs[72]. Thus, finding poor quality CPGs is not confined to this area of healthcare[73]. Improvement messages are generalisable to other specialties.

Meaning of the study: possible explanations

The finding of higher-quality, but narrow, focus on gender minority/trans people's healthcare for blood-borne infections may relate to the global HIV pandemic and the WHO applying twin lenses of public health and human rights (i.e. the population as 'means' and 'ends'). The lower-quality CPGs focus on transition. WPATH SOCv7[30] originated nearly a decade ago from a special-interest association, diagnostic criteria and CPG methodology have since changed. Although HIV and transition are important, it is puzzling to have found so little else, maybe suggesting CPGs for gender minority/trans people have been driven by provider-interests rather than healthcare needs. Including gender minority/trans people in guidelines can be considered a matter of health equity, where CPGs have a role to play[74]. GRADE suggests CPG developers may consider equity at various stages in creating guidelines, such as deciding guideline questions, evidence searching, and assembly of the guideline group[75]. How CPGs may impact more vulnerable members of society should be reflected-upon during guideline development[76], and implementation[77].

Implications for clinicians, UK and international policymakers, and patients

Clinicians should be made aware that gender minority/trans health CPGs outside of HIV-related topics are linked to a weak evidence base, with variations in methodological rigour and lack of stakeholder involvement. While patient care plans ought to take into account the individual needs of each gender minority/trans person, a gap appears to exist

between clinical practice and research in this field[78]. Clinicians should proceed with caution, explain uncertainties to patients and recruit to research.

Policymakers ought to invest in both primary research and high-quality systematic reviews in areas relevant for CPG and service development. Organisations producing guidelines and aspiring to higher-level quality could use more robust methods, handling of competing interests[79,80], and quality assessment. CPG developers should label key recommendations clearly. Although editorial independence was lowest priority for stakeholders, independent external review is important to avoid biases and bad practices, examine use of resources, resist commercial interests, and gain widespread credibility outside the field.

The UK is fortunate in being familiar with developing priority-setting partnerships (e.g. James Lind Initiative[81]) and generating suites of clinical questions that might cover all steps in patient pathways (e.g. in partnership with Cochrane Collaboration[82]). These could underpin multidisciplinary and funded research priorities whose results feed into future better evidence-based CPGs. Implications for UK education and curricular content (e.g. new gender identity healthcare credentials[83]), should be carefully scrutinised.

Internationally, CPG development and implementation will vary depending on local country contexts and available resources. Those countries with quality assurance agencies might use them for external assurance. Countries might reconsider the wisdom of adapting low-quality 'off the shelf' international CPGs without due assessment of the evidence for recommendations (e.g. using the GRADE Adolopment framework[84]). WHO demonstrates how CPGs can achieve high quality.

Patients should be positively encouraged to engage with CPG development as stakeholders. The lack of patient-facing material should be addressed, especially as medical and non-medical online material contains jargon, is unreliable and potentially misleading[85]. Future CPGs should be populated with patient-facing decision aids (e.g. Fact Boxes[86] and icon arrays[87]) that explain sizes of benefits and harms to support informed patient choice. Patients and carers will benefit from a more focused approach to throughout-life healthcare. As the figures for gender minority/trans patients increase within the NHS and internationally, so does the need for consistent guidance to clinicians across specialisms on specific risks to, and means of treating, this population. Current patients should be welcomed to contribute, where they are comfortable, to any research being undertaken by their clinicians, in order to improve data and future practice for gender minority/trans health.

Unanswered questions and future research

This study should be replicated as new iterations of international CPGs become available. It can be applied to national guidelines and countries should perform their own stakeholder prioritisation. When 'best available evidence' is poor, quality improvement can be driven both from inside and outside the field. International guideline developers require more primary research for this population, and impetus from clinicians and scientists to build a better evidence base using robust data from randomised controlled trials and long-term observational cohort studies, especially regarding chronic diseases, health behaviours, substance use, screening and how interventions (e.g. hormones) might impact on long-term health (e.g. risk of cardiovascular and thromboembolic disease).

Mortality and QoL data are required to address questions of clinical and cost-effectiveness.

Conclusion

Gender minority/trans health in current international CPGs seems limited to a focus on HIV or transition-related interventions. WPATH SOCv7[30] is due for updating and this study should be used positively to accelerate improvement. Future guideline developers might better address the holistic healthcare needs of gender minority/trans people by enhancing the evidence-base, upgrading the quality of CPGs and increasing the breadth of health topics wherein this population is considered.

Compliance with Ethical Standards

Contributorship statement: The authors were involved as follows: SB, IA, CM conception. All authors (SD, DC, IA, MJ, SB, CM) were involved in design, execution, analysis, drafting manuscript and critical discussion; all were responsible for revision and final approval of the manuscript. All authors had full access to all the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. CM acts as guarantor.

Competing interests statement: The authors had no financial support for this work. There were no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years and there were no other relationships or activities that could appear to have influenced the submitted work. All authors declare they have no conflict of interests. SB, SD & DC's declarations can be found at http://www.whopaysthisdoctor.org

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Dissemination plan: Not applicable, publication will be shared with stakeholders.

Transparency declaration: CM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned and registered have been explained.

Licence Statement

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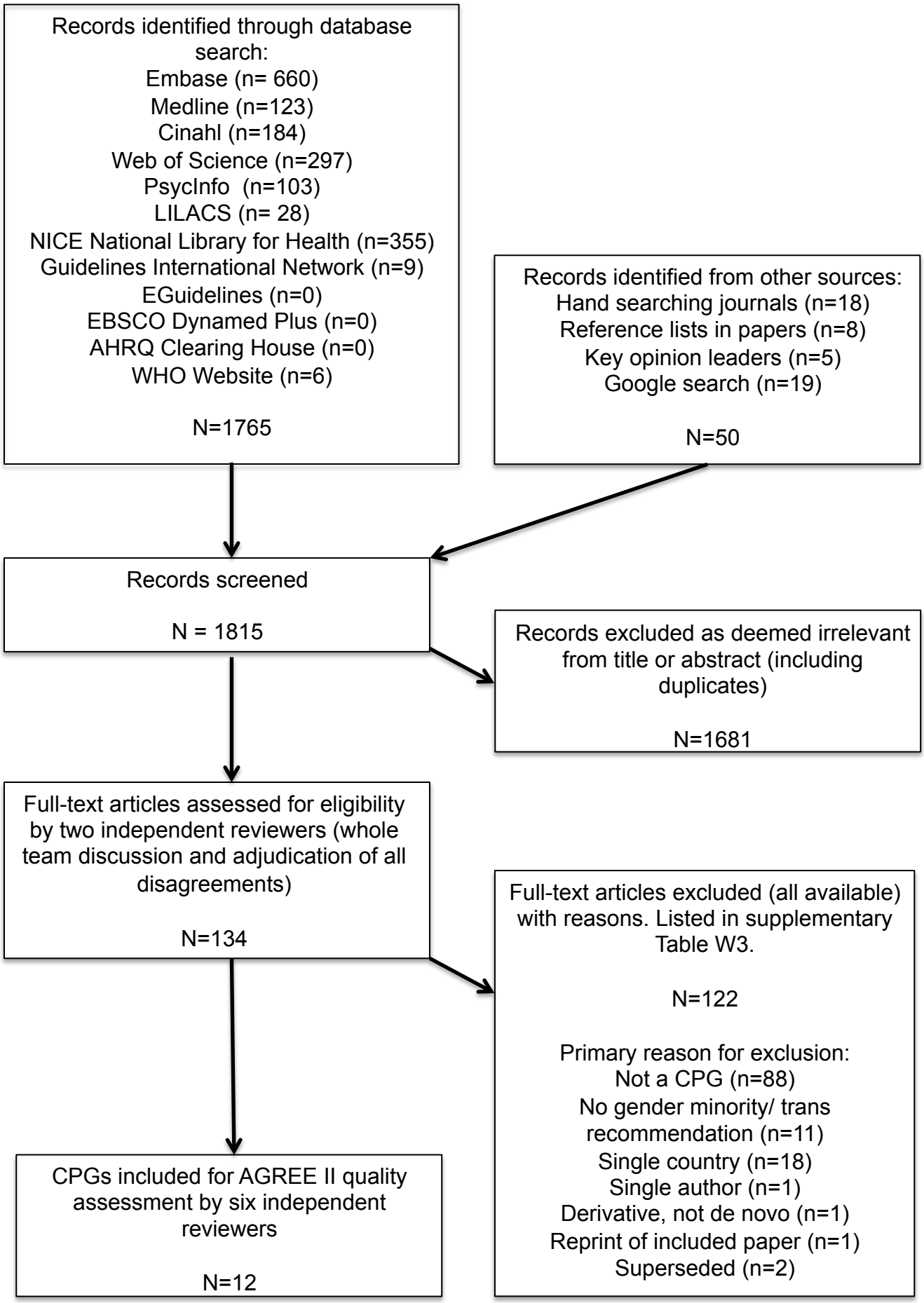
Legend/Key for Figure

Figure 1. PRISMA flow diagram

Key: CPG, clinical practice guideline; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses


Records identified through database search:
Embase (n= 660)
Medline (n=123)
Cinahl (n=184)
Web of Science (n=297)
PsycInfo (n=103)
LILACS (n= 28)
NICE National Library for Health (n=355)
Guidelines International Network (n=9)
EGuidelines (n=0)
EBSCO Dynamed Plus (n=0)
AHRQ Clearing House (n=0)
WHO Website (n=6)
N=1765
Records identified from other sources:
Hand searching journals (n=18)
Reference lists in papers (n=8)
Key opinion leaders (n=5)
Google search (n=19)
N=50
Records screened
N = 1815
Records excluded as deemed irrelevant from title or abstract (including duplicates)
N=1681
Full-text articles assessed for eligibility by two independent reviewers (whole team discussion and adjudication of all disagreements)
N=134
Full-text articles excluded (all available) with reasons. Listed in supplementary Table W3.
N=122
Primary reason for exclusion:
Not a CPG (n=88)
No gender minority/ trans recommendation (n=11)
Single country (n=18)
Single author (n=1)
Derivative, not de novo (n=1)
Reprint of included paper (n=1)
Superseded (n=2)
CPGs included for AGREE II quality assessment by six independent reviewers
N=12

International Clinical Practice Guidelines for Gender Minority/Trans People: Systematic Review and Quality Assessment

Supplementary/ Web/ Appendices

W1. Search terms used and search strategy for at least one database

W2. Stakeholder and review team priority scoring exercise

W3. Full text excluded studies with reasons for exclusion

W4. Extracted sentences relating to mortality or quality of life with associated references from Clinical Practice Guidelines

W5. Extracted key recommendations from Clinical Practice Guidelines

W1: Literature searching – Databases searched and search terms used

Embase <1974 to 2019 July 29>

1 transgender.mp. or transgender/ (7297)
2 transsexual.mp. (2070)
3 gender identity/ or gender non-conforming.mp. (15929)
4 non-binary.mp. (219)
5 gender minority.mp. or "sexual and gender minority"/ (1582)
6 transman.mp. (20)
7 transwoman.mp. (25)
8 gender dysphoria.mp. or gender dysphoria/ (1887)
9 gender diversity.mp. (257)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (24836)
11 practice guideline/ or clinical guideline.mp. (387400)
12 10 and 11 (511)
13 limit 12 to yr="2008 - 2020" (460)

Ovid MEDLINE(R) ALL <1946 to July 29, 2019>

1 gender diversity.mp. (225)
2 gender dysphoria.mp. or Transsexualism/ or Gender Dysphoria/ or Gender Identity/ (20817)
3 gender minority.mp. or "Sexual and Gender Minorities"/ (2406)
4 Transgender Persons/ or gender non-conforming.mp. (2429)
5 non-binary.mp. (164)
6 transgender.mp. (5364)
7 transman.mp. (8)
8 transwoman.mp. (13)
9 Transsexualism/ or transsexual.mp. (3855)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (26619)
11 Practice Guidelines as Topic/ or clinical guideline.mp. (112006)
12 10 and 11 (103)

Web of Science

Search terms: (TOPIC: (((((transgender OR gender dysphoria) OR transsexual) OR gender identity) OR transman) OR transwomen) AND TOPIC: (clinical guideline OR practice guideline)) [271 results]

(TOPIC: (gender incongruence) AND TOPIC: (clinical guideline OR practice guideline))

NICE Evidence

Search terms: Transgender, gender dysphoria

CINAHL
(transgender or transsexual or transsexual or gender variant or gender non-conforming or transmen or transwomen or gender dysphoria or gender identity) AND (clinical guideline or practice guideline)

PSYCInfo
(transgender or transsexual or transexual or gender variant or gender non-conforming or transmen or transwomen or gender dysphoria or gender identity) AND (clinical guideline or practice guideline)

AHRQ National Guidelines Clearing House
Search terms: trans, gender identity. Was stopped in 2018 – no update searches available

eGuidelines
Search terms: trans, gender identity

Guidelines International Network
Search terms: Transgender, gender dysphoria, gender identity

WHO website – not searchable on so used Google instead

Google Search terms: WHO transgender guidelines - First 100 hits examined

Update: WHO transgender guidelines 2020

LILACS
Search term: gender dysphoria

W2: Stakeholder prioritisation exercise and comparison with research team

Domains	Stakeholders (n=19) #						Reviewers (n=6)					
Priority	**1 highest**	**2**	**3**	**4**	**5**	**6 lowest**	**1 highest**	**2**	**3**	**4**	**5**	**6 lowest**
Scope and purpose	***	***** *	*	**	***** *		*	*	*****	**		*
Stakeholder Involvement	***** ****	*	***	**	**	*			*	*	**	*
Rigour of development	*	*	*****	*****	****	**	*****	*				
Clarity and presentation	***	***	*****	***	*	***		*		***	*	
Applicability	*	***** **	**	*****	***			*			*	***
Editorial independence	**	*	**	*		***** ***** *		**			**	*

Key: # Numbers do not all add up to 19 as one stakeholder only gave first two preferences; * stakeholder or reviewer preference vote. Green shows highest priority and red shows lowest priority

W3: Excluded full studies with reasons for exclusion

Full Citation (n=122)	Reason(s) for exclusion
Ackerley CG, Poteat T, Kelley CF. Human Immunodeficiency Virus in Transgender Persons. *Endocrinol Metab Clin North Am* 2019;**48**:453–64. doi:10.1016/j.ecl.2019.02.007	Not a CPG. Single country.
Adams N, Pearce R, Veale J, *et al.* Guidance and Ethical Considerations for Undertaking Transgender Health Research and Institutional Review Boards Adjudicating this Research. *Transgender Heal* 2017;**2**:165–75. doi:10.1089/trgh.2017.0012	Not a CPG.
ADFAM. Including diverse families: good practice guidelines. 2010. https://adfam.org.uk/files/docs/idf_toolkit.pdf	No TG specific recommendation. Single country.
Akl EA, Kennedy C, Konda K, *et al.* Using GRADE methodology for the development of public health guidelines for the prevention and treatment of HIV and other STIs among men who have sex with men and transgender people. *BMC Public Health* 2012;**12**:386. doi:10.1186/1471-2458-12-386	Not a CPG.
American College of Obstetricians and Gynecologists, Sokkary N, Gomez-Lobo V. Committee Opinion No. 685: Care for Transgender Adolescents. *Obstet Gynecol* 2017;**129**:e11–6. doi:10.1097/AOG.0000000000001861	Not a CPG. Single country.
American Psychological Assoc. Guidelines for psychological practice with transgender and gender nonconforming people. *Am Psychol* 2015;**70**:832–64. doi:10.1037/a0039906	Single country.
American Psychological Association. Multicultural guidelines: An ecological approach to context, identity, and intersectionality, 2017. *Am Psychol Assoc*: 2017.http://www.apa.org/about/policy/multicultural-guidelines.pdf	Single country.
American Society for Reproductive Medicine, American College of Obstetricians and Gynecologists. Prepregnancy counseling: Committee Opinion No. 762. *Fertil Steril* 2019;**111**:32–42. doi:10.1016/j.fertnstert.2018.12.003	Not a CPG. No TG specific recommendation. Single country.
Baggaley R, Armstrong A, Dodd Z, *et al.* Young key populations and HIV: A special emphasis and consideration in the new WHO Consolidated Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations. *J Int AIDS Soc* 2015;**18**:85–8. doi:10.7448/IAS.18.2.19438	Not a CPG.
Barrett J. Gender Dysphoria in Adults. BMJ Best Pract. 2018.https://bestpractice.bmj.com/topics/en-gb/992	Not a CPG. Single author.
Bekker L-G, Rebe K, Venter F, *et al.* Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV-1 infection. *South Afr J HIV Med* 2016;**17**. doi:10.4102/sajhivmed.v17i1.455	Single country.
Berli JU, Capitán L, Simon D, *et al.* Facial gender confirmation surgery—review of the literature and recommendations for Version 8 of the WPATH Standards of Care. *Int J Transgenderism* 2017;**18**:264–70. doi:10.1080/15532739.2017.1302862	Not a CPG.
Bhugra D, Gupta S, Schouler-Ocak M, *et al.* EPA Guidance Mental Health Care of Migrants. *Eur Psychiatry* 2014;**29**:107–15. doi:10.1016/j.eurpsy.2014.01.003	Not a CPG. No TG specific recommendation.
Bonifacio JH, Maser C, Stadelman K, *et al.* Management of gender dysphoria in adolescents in primary care. *Can Med Assoc J* 2019;**191**:E69–75. doi:10.1503/cmaj.180672	Not a CPG. Single country.
Bonnington A, Dianat S, Kerns J, *et al.* Society of Family Planning clinical recommendations: Contraceptive counseling for transgender and gender diverse people who were female sex assigned at birth. *Contraception* Published Online First: 2020. doi:10.1016/j.contraception.2020.04.001	Single country.
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Key: CPG = clinical practice guideline; TG = trans people/gender minority

W4: Extracted sentences relating to mortality or quality of life with associated references from Clinical Practice Guidelines

	Author (yr)	In-text statement on Mortality/ Quality of Life (QoL)	Page	References
1	Coleman et al. (2012)	**Mortality:** Two long-term observational studies, both retrospective, compared the mortality & psychiatric morbidity of transsexual adults to those of general population samples (Asscheman et al., 2011; Dhejne et al., 2011). An analysis of data from the Swedish National Board of Health & Welfare information registry found that individuals who had received sex reassignment surgery (191 MtF & 133 FtM) had significantly higher rates of mortality, suicide, suicidal behavior, & psychiatric morbidity than those for a nontranssexual control group matched on age, immigrant status, prior psychiatric morbidity, & birth sex (Dhejne et al., 2011). Similarly, a study in the Netherlands reported a higher total mortality rate, including incidence of suicide, in both pre- & post-surgery transsexual patients (966 MtF and 365 MtF) than in the general population of that country (Asscheman et al., 2011). Neither of these studies questioned the efficacy of sex reassignment; indeed, both lacked an adequate comparison group of transsexuals who either did not receive treatment or who received treatment other than genital surgery. Moreover, transsexual people in these studies were treated as far back as the 1970s. However, these findings do emphasize the need to have good long-term psychological & psychiatric care available for this population. More studies are needed that focus on the outcomes of current assessment & treatment approaches for gender dysphoria.	108	Asscheman H, Giltay EJ, Megens JAJ, *et al.* A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol* 2011;**164**:635–42. doi:10.1530/EJE-10-1038 Dhejne C, Lichtenstein P, Boman M, *et al.* Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden. *PLoS One* 2011;**6**:e16885. doi:10.1371/journal.pone.0016885
		QoL: One troubling report (Newfield et al., 2006) documented lower scores on QoL (measured with the SF-36) for FtM patients than for the general population. A weakness of that study is that it recruited its 384 participants by a general email rather than a systematic approach, and the degree and type of treatment were not recorded. Study participants who were taking testosterone had typically being doing so for less than 5 years. Reported QoL qas higher for patients who had undergone breast/chest surgery than for those who had not (p<.001). (A similar analysis was not done for genital surgery.)	108	Newfield E, Hart S, Dibble S, *et al.* Female-to-male transgender quality of life. *Qual Life Res* 2006;**15**:1447–57. doi:10.1007/s11136-006-0002-3
		QoL: In other work, Kuhn & colleagues (2009) used the King's Health Questionnaire to assess the quality of life of 55 transsexual patients at 15 years after surgery. Scores were compared to those of 20 healthy female control patients who had undergone abdominal/pelvic surgery in the past. Quality of life scores for transsexual patients were the same or better than those of control patients for some subscales (emotions, sleep, incontinence, symptom severity, and role limitation), but worse in other domains (general health, physical limitation, and personal limitation).	108	Kuhn A, Bodmer C, Stadlmayr W, *et al.* Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertil Steril* 2009;**92**:1685-1689.e3. doi:10.1016/j.fertnstert.2008.08.126
2	Davies et al. (2015)	**QoL:** A number of studies indicate that speech-therapy intervention is useful in helping gender nonconforming individuals portray their gender identity through speech (Carew, Dacakis, & Oates, 2007; Dacakis, Oates, & Douglas, 2012; Gelfer & Tice, 2013; Hancock & Garabedian, 2013; Meszaros et al., 2005). Such changes to communication are not simply superficial; they can reduce gender dysphoria and improve mental health and quality of life.	117-118	Carew L, Dacakis G, Oates J. The Effectiveness of Oral Resonance Therapy on the Perception of Femininity of Voice in Male-to-Female Transsexuals. *J Voice* 2007;**21**:591–603. doi:10.1016/j.jvoice.2006.05.005 Dacakis G, Oates J, Douglas J. Beyond voice. *Curr Opin*

				Otolaryngol Head Neck Surg 2012;**20**:165–70. doi:10.1097/MOO.0b013e3283530f85 Gelfer MP, Tice RM. Perceptual and Acoustic Outcomes of Voice Therapy for Male-to-Female Transgender Individuals Immediately After Therapy and 15 Months Later. *J Voice* 2013;**27**:335–47. doi:10.1016/j.jvoice.2012.07.009 Hancock AB, Garabedian LM. Transgender voice and communication treatment: a retrospective chart review of 25 cases. *Int J Lang Commun Disord* 2013;**48**:54–65. doi:10.1111/j.1460-6984.2012.00185.x Mészáros K, Csokonai Vitéz L, Szabolcs I, *et al.* Efficacy of Conservative Voice Treatment in Male-to-Female Transsexuals. *Folia Phoniatr Logop* 2005;**57**:111–8. doi:10.1159/000083572 * Hancock AB, Krissinger J, Owen K. Voice Perceptions and Quality of Life of Transgender People. *J Voice* 2011;**25**:553–8. doi:10.1016/j.jvoice.2010.07.013
3	ECDC (2018)	**Mortality:** the World Health Organization (WHO) and UNAIDS have identified several targets along the continuum of care for hepatitis B virus (HBV), hepatitis C virus (HCV) and HIV. These *include* promoting early diagnosis, scaling up treatment and reducing disease-related mortality [12,13].	3	12. World Health Organization. Global health sector strategy on viral hepatitis 2016–2021: towards ending viral hepatitis. Geneva: WHO; 2016. 13. World Health Organization. Global health sector strategy on HIV, 2016–2021: towards ending AIDS. Geneva: WHO; 2016.
		QoL (as QALY): Since then, the feasibility of birth cohort testing for HCV has been studied in several European countries, including Ireland, Italy, and Spain [87–89]. In the studies in Ireland and Spain, the authors concluded that to effectively implement birth cohort testing for HCV, each country must determine its own HCV seroprevalence by year in order to successfully develop screening recommendations because risk factors, particularly injecting drug use, can affect the selection of birth cohort. In Italy, authors found that the anti-HCV screening program had an acceptable expenditure increase for the National Health Service compared to the cost per quality-adjusted life year (QALY) of other approved interventions or treatments in Italy."	18	87. Group HCSGD. Background to recommendation 20: general population or birth cohort screening. Dublin: Health Protection Surveillance Centre; 2017. 88. Ruggeri M, Coretti S, Gasbarrini A, Cicchetti A. Economic assessment of an anti-HCV screening program in Italy. Value Health. 2013;16(6):965–72. 89. Mena A, Moldes L, Meijide H, Canizares A, Castro-Iglesias A, Delgado M, et al. Seroprevalence of HCV and HIV infections by year of birth in Spain: impact of US CDC and USPSTF recommendations for HCV and HIV testing. PLoS ONE. 2014;9(12):e113062.
		QALY: Four cost implication studies of HIV testing in hospital settings have been conducted in UK. They show that universal offer testing was highly cost effective if future healthcare costs & QALYs are incorporated into calculations [236-239]	23	236. Ong KJ, Thornton AC, Fisher M, Hutt R, Nicholson S, Palfreeman A, et al. Estimated cost per HIV infection diagnosed through routine HIV testing offered in acute general medical admission units and general practice settings in England. HIV Medicine. 2016;17(4):247-54. 237. Pizzo E, Rayment M, Thornton A, Rae C, Hartney T, Delpech V, et al. Cost-effectiveness analysis of HIV testing in non-traditional settings-the HINTS study. HIV Medicine. 2014;15:93. 238. Sewell J, Capocci S, Johnson J, Solamalai A, Hopkins S, Cropley I, et al. Expanded blood borne virus testing in a

				tuberculosis clinic. A cost and yield analysis. J Infect. 2015;70(4):317-23. 239. Alexander H, Brady M, Poulton M. A calculation of the financial impact of opt-out HIV testing in a London Emergency Department (ED). HIV Med. 2016 April.
4	Gilligan et al. (2017)	**Mortality/QoL:** no statements linked to references		
5	Hembree et al. (2017)	**Mortality:** Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (161). … The largest cohort of transgender females (mean age 41 years, followed for a mean of 10 years) showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (161).	3891	161. van Kesteren PJM, Asscheman H, Megens JAJ, Gooren LJG. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf). 1997;47(3): 337–343.
		Mortality: A systematic review of the literature found that data were insufficient (due to very low–quality evidence) to allow a meaningful assessment of patient-important outcomes, such as death, stroke, myocardial infarction, or VTE in transgender males (176). Future research is needed to ascertain the potential harm of hormonal therapies (176).	3895	176. Elamin MB, Garcia MZ, Murad MH, Erwin PJ, Montori VM. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. Clin Endocrinol (Oxf). 2010;72(1):1–10.
		Mortality: Another analysis demonstrated that, despite the young average age at death following surgery and the relatively larger number of individuals with somatic morbidity, the study does not allow for determination of causal relationships between, for example, specific types of hormonal or surgical treatment received and somatic morbidity and mortality (263).	3895	**263. Djordjevic ML, Bizic MR, Duisin D, Bouman MB, Buncamper M. Reversal Surgery in regretful male-to-female transsexuals after sex reassignment surgery. J Sex Med. 2016;13(6):1000–1007. *Note title of reference 262:* *262. Simonsen RK, Hald GM, Kristensen E, Giraldi A. Long-term follow-up of individuals undergoing sex-reassignment surgery: somatic morbidity and cause of death. Sex Med. 2016;4(1): e60–e68.*
		QoL: Likewise, a meta-analysis of 19 randomized trials in nontransgender males on testosterone replacement showed no increased incidence of cardiovascular events (185).	3891	185. Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, Bhasin S. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci. 2005;60(11):1451–1457.
6	IAPHCCO (2015)	**Mortality:** The Strategic Timing of AntiRetroviral Treatment (START) study recently showed a 53% reduction in serious morbidity and mortality from HIV due to early ART at CD4 counts of over 500 cells/mm3 (96)	6	96. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373(9):795–807.
		Mortality Increasing early access to ART is associated with decreased AIDS-related morbidity and mortality, as well as reduced risk of HIV transmission (167)	8	167. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. Lancet Infect Dis. 2014;14(4):281–290.
		Mortality: Antiretroviral therapy is proven to prevent HIV-related morbidity, mortality, and transmission.(7)	9	7. Montaner JS, Lima VD, Harrigan PR, et al. Expansion of HAART coverage is associated with sustained decreases in HIV/AIDS morbidity, mortality and HIV transmission: the ‘‘HIV Treatment as Prevention’’ experience in a Canadian setting. PLoS One. 2014; 9(2):e87872.

		Mortality: Community-located ART distribution is a cost-effective service delivery model whose rates of attrition and mortality are similar to those at the facility level. (195,196)	10	195. Kredo T, Ford N, Adeniyi FB, Garner P. Decentralising HIV treatment in lower- and middle-income countries. Cochrane Database Syst Rev. 2013;6:CD009987. 196. Chu C, Umanski G, Blank A, Grossberg R, Selwyn PA. HIVinfected patients and treatment outcomes: an equivalence study of community-located, primary care-based HIV treatment vs. hospital-based specialty care in the Bronx, New York. AIDS Care. 2010;22(12):1522–1529.
		Mortality In Uganda, ART distribution at community-based sites was found to be associated with significantly higher rates of retention in care and lower mortality rates. (88, 204)	10	88. Wamboga Magawa J, Mpiima D. Community ART Delivery Model for High Retention of Patients on Antiretroviral Therapy: The AIDS Support Organisation (TASO) Operational Research Findings East and Central Uganda, Resource-Limited Setting. Presented at: 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention; June 30-July 3, 2013; Kuala Lumpur, Malaysia. 204. Grimsrud A, Patten G, Sharp J, Myer L, Wilkinson L, Bekker LG. Extending dispensing intervals for stable patients on ART. J Acquir Immune Defic Syndr. 2014;66(2):e58–e60.
		Mortality /QoL: Today, a person diagnosed with HIV at the age of 20 years if started promptly on ART is expected to live a normal life span, with a highly preserved quality of life.(1)	1	1. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One. 2013; 8(12):e81355.
		QoL: Stigma can negatively shape quality of life, affect mental health, and influence ART use and outcomes. **QoL:** Mental health disorders such as these can result in a poorer quality of life and negatively affect access to and use of HIV services."	5	No linked reference
		QoL: Impact of actions taken to reduce stigma & discrimination & address mental health from a quality-of-life perspective (eg, interventions and programs) on these issues as well as on HIV-related health outcomes.	18	No linked reference
7	Ralph et al (2010)	**Mortality/QoL:** no statements linked to references		
8	Strang et al (2016)	**Mortality/QoL:** no statements linked to references		
9	T'Sjoen et al (2020)	**QoL:** Although the quality of sexual life improves after GAMI, research has demonstrated that it does not reach the levels of cisgender people.(44)	575	44. Nobili A, Glazebrook C, Arcelus J. Quality of life of treatment seeking transgender adults: a systematic review and metaanalysis. Rev Endocr Metab Disord 2018;19:199-220.
		QoL: Overall results lean toward favorable sexual outcomes after genital surgeries in trans people, although research into the quality of sexual life in the trans population after GAMI is limited.(44)	580	44. Nobili A, Glazebrook C, Arcelus J. Quality of life of treatment seeking transgender adults: a systematic review and metaanalysis. Rev Endocr Metab Disord 2018;19:199-220.
10	WHO (2011)	**Mortality**: A systematic literature search was conducted on the role of HTC in reducing HIV-related morbidity and mortality, compared with the provision of basic information on HIV prevention and care. The surrogate outcomes were behavioural change and HIV incidence.	39	No direct reference, appears to relate to the systematic review

		Mortality: Alcohol and substance use/dependence is a problem for many MSM and transgender people, and is linked to significant morbidity and mortality.(52)	53	52. Stall R et al. Alcohol use, drug use and alcohol-related problems among men who have sex with men: the Urban Men's Health Study. Addiction, 2001, 96:1589–1601.
		Mortality: OST has been demonstrated to improve both access and adherence to ART, and reduce mortality.(120)	54	120. WHO, UNODC, UNAIDS. *Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users, including access to needle syringe programmes*. Geneva, WHO, 2009. http:// www.unodc.org/documents/hiv-aids/idu_target_setting_guide.pdf (accessed 13 April 2011).
		Mortality: Antiretroviral therapy (ART) is the core pharmacological component of a broad and comprehensive management of HIV infection. ART has significantly decreased the morbidity and mortality from HIV in the past decades. Given that ART represents a biologically targeted intervention, where sexual identities play a minimal role or no role at all on expected effects, there is no reason, biological or other, to differentiate ART recommendations for MSM and transgender people from those formulated for other populations (excluding HIV-infected pregnant women and newborns).	57	No direct reference, appears to come from the systematic review
		QoL: There was no evidence available on issues of quality of life such as inconvenience or decreased desire; however, the values and preferences of the MSM polled by MSMGF showed support for this intervention.(66)	33	66 Arreola S et al. *In our own words: preferences, values, and perspectives on HIV prevention and treatment – a civil society consultation with men who have sex with men and transgender people*. Oakland, California, The Global Forum on MSM and HIV (MSMGF), 2010. http://msmgf.org/files/msmgf//About_Us/Publications/WHO_Report 1.pdf (accessed 19 May 2011)
		QoL: No considerations regarding quality of life such as inconvenience or decreased sexual desire were studied.	35	No direct reference, appears to come from the systematic review
		QoL: No studies were found with information on issues related to quality of life due to the intervention.	44	No direct reference, appears to come from the systematic review
		QoL: Quality of life (inconvenience, unnecessary intervention, anxiety and discrimination) was not measured.	44	No direct reference, appears to come from the systematic review
		QoL: None of the studies reported on HIV or STI incidence or quality of life.	46	No direct reference, appears to come from the systematic review
		QoL: People living with HIV, regardless of ART indication, should also benefit from basic HIV prevention and care, including effective interventions that are simple, relatively inexpensive, improve the quality of life, prevent further transmission of HIV or common opportunistic infections, delay progression of HIV disease and prevent mortality.	59	No linked reference
11	WHO (2012)	**QoL (as QALY):** Using sexual risk behaviour data from the Partners in Prevention trial *(16)*, the cost per HIV infection averted was between US$6000 and $66 000 when PrEP was always used, and the savings per quality-adjusted life year (QALY), a standard measure of cost-benefit, was $260 to $4900. Using "more typical" data that assume less risky sexual behaviour, the cost per HIV infection averted was between ~$0 (break-even) and $26 000 when PrEP was always used, and the cost per QALY gained was between minus $200 (cost-	7	16. Celum C et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. New England Journal of Medicine, 2010, 362(5):427–439.

		saving) and $1900.		
		QoL (as QALY): One cost-effectiveness study in Australia estimated that, if continuous use of PrEP was 90% effective and the program covered only HIV-negative MSM having high-risk sex, it would cost US$47 745 per QALY gained *(18)*. Another cost-effectiveness study from the USA estimated that if PrEP was 90% effective and the program covered only HIV-negative MSM having high-risk sex, it would cost US$107 000 per QALY gained *(19)*. If PrEP was 50% effective, it would cost US$298 000 per QALY gained. Sensitivity analyses showed that the cheaper and more efficacious PrEP is and the more high-risk the population is, the more cost-effective that PrEP would be, with estimates in cost-saving ranging up to over US$300 000 per QALY gained *(20)*. Overall, cost-effectiveness estimates vary widely, depending on model parameter estimates, including efficacy, cost of PrEP, HIV incidence and age of the population.	10-11	18. Anderson J, Cooper D. Cost-effectiveness of pre-exposure prophylaxis for HIV in an MSM population. HIV Medicine, 2009, 10:39. 19. Desai K et al. Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness. AIDS, 2008, 22(14):1829–1839. 20. Paltiel AD et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. Clinical Infectious Diseases, 2009, 48(6):806–815.
12	WHO (2016)	**Mortality:** Access and adherence to OST can improve health outcomes (4), reduce overdose and resulting mortality (54)	33	4. Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, World Health Organization, 2013 and Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, WHO, 2015 (http://www.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf, accessed 25 February 2014). and Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, WHO, 2015. http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf?ua=154. Spire B, Lucas GM, Carrieri MP. Adherence to HIV treatment among IDUs and the role of opioid substitution treatment (OST). International Journal of Drug Policy, 2007, 18(4):262–270 (https://www.plhivpreventionresources.org/index.cfm?action=main.abstract&id=1460 accessed 28 February 2014).
		Mortality: Provision of OST before release can help reduce overdose-related mortality (61).	35	61. Degenhardt L et al. What has been achieved in HIV prevention, treatment and care for people who inject drugs, 2010-2012? A review of the six highest burden countries. International Journal of Drug Policy, 2014, 25:53–60 (http://www.sciencedirect.com/science/article/pii/S095539591300128X, accessed 27 February 2014).
		Mortality: Completing TB treatment is critical to reducing mortality and avoiding the development and spread of drug-resistant TB. It is vital to provide a supportive, non-judgemental and non-discriminatory environment that enables people from key populations to complete treatment, provides additional adherence support measures to improve treatment outcomes, and reduces the risk of continued TB transmission (65). Timely initiation of ART significantly reduces the risk of mortality from HIV-associated TB.	64	65. Policy guidelines for collaborative TB and HIV services for injecting and other drug users: an integrated approach. Geneva, World Health Organization, 2008 (Evidence for Action Technical Papers) (http://whqlibdoc.who.int/publications/2008/9789241596930_eng.pdf accessed 25 February 2014). Integrating collaborative TB and HIV services within a comprehensive package of care for people

				who inject drugs.- Consolidated guidelines. Geneva, WHO, 2016. http://www.who.int/tb/publications/integrating-collaborative-tb-and-hiv_services_for_pwid/en/
		Mortality: Among those living with HIV who are coinfected with HBV or HCV, liver disease progresses more rapidly and mortality is greater than among those with HBV or HCV who are not living with HIV.	67	No linked reference
		Mortality: Coinfection with HIV and HCV accelerates HCV-related progression of liver fibrosis and leads to a higher rate of end-stage liver disease and mortality (121, 151, 157).	68	121. Benhamou Y et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. Hepatology, 1999, 30:1054–1058. 151. Deng LP et al. Impact of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. World Journal of Gastroenterology, 2009, 15:996–1003. 157. Pineda JA et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. Hepatology, 2005, 41:779–789.
		Mortality: These effects may be magnified in low-income and food-insecure contexts, such as those experienced by many key populations. In turn, poor nutritional status can hasten the progression of HIV disease; low body mass index (BMI) in adults (BMI less than 18.5 kg/m2) is an independent risk factor for HIV disease progression and mortality (4).	73	4. Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, World Health Organization, 2013 and Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, WHO, 2015 (http://www.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf, accessed 25 February 2014). and Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, WHO, 2015. http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf?ua=1

Key: ART, antiretroviral therapy; GAMI, gender affirming medical intervention; HIV, human immunodeficiency virus; HTC, HIV testing and counselling; MSM, men who have sex with men; OST,opiate substitution therapy; PrEP, pre-exposure prophylaxis; QALY, Quality-Adjusted Life Year; TB, tuberculosis; * Reference appears in reference list, but not in the main text; ** We believe there is an error here and that the morbidity statement refers to ref 262 not 263. Also noted that references 260 and 261 were the wrong way around.

W5. Extracted Key Recommendations from Clinical Pratice Guidelines

Author (year)	Recommendations
Coleman et al. (2012)	None. Reviewer team were unable to extract key recommendations
Davies et al. (2015)	*Voice and Communication Intervention for Gender Nonconforming Individuals* 1.Transgender voice and communication services should be offered in the context of a complete approach to transgender health that includes comprehensive primary care and a coordinated approach to psychological and social issues. 2.In working with gender nonconforming clients, the speech-language therapist's primary goal is to help the client develop voice and communication that more closely approximates the client's sense of self. 3.Feminizing/masculinizing voice involves nonhabitual use of the voice-producing mechanism. To prevent the possibility of vocal damage, professional evaluation and assistance are essential. 4.Self-guided voice and communication change without professional supervision is not recommended. Clients intending to pursue self-guided voice change should be encouraged to, at a minimum, have an initial professional assessment and then to consult with their primary care provider if they develop symptoms of vocal fatigue or negative changes to vocal quality. Self-help voice and communication groups should have appropriate clinical support. *Clinical Competence* 1.Voice and communication professionals working with transgender individuals must have a basic understanding of transgender health (including hormonal and surgical feminization/masculinization) and trans-specific psychosocial issues; they must be familiar with basic sensitivity protocols such as use of preferred gender pronoun and name. 2.Gender nonconforming individuals who are seeking voice and communication services for reasons other than speech feminization/masculinization can be treated by trans-sensitive speech-language therapists using standard voice and communication protocols. voice and communication feminization/masculinization requires additional clinical expertise and special clinical protocols. *Client Inclusion and Exclusion* 1.Voice and communication services should be available to the full spectrum of the transgender community, including MtF and MtF transsexuals and others who are gender nonconforming. 2.The need for voice and communication services should not be evaluated based on hormonal use, pursuit of sex reassignment surgery, or length or percentage of time living in the desired gender role. 3.Services should be adapted as needed to fit a client's individual needs, including accommodation relating to speech or hearing disability, mental illness, cognitive disability, learning disability, physical disability, geographic isolation, or incarceration. *Treatment Decisions* 1.The client is responsible for treatment decisions, supported by the clinician's informed professional opinion, assessment data, and any allies the client wishes to be involved. To support fully informed treatment decisions, clients should be informed of the following: a.potential risks and benefits associated with treatment options b. estimated duration of treatment; factors that can influence the duration of treatment 2. Existing protocols for voice and communication feminization should be reviewed and considered when developing individualized treatment plans. As there are no established protocols for speech masculinization, FtMs seeking this service should be informed that the protocol is a trial. 3. While modification of existing protocols is encouraged, all treatment plans (including those using new or experimental techniques) are expected to be based on a clearly articulated, logical, and valid clinical rationale. Departure from existing protocols should be explained as such to the client as part of fully informed consent and should be documented in detail to facilitate evaluation. *Assessment* 1.Assessment prior to voice and communication feminization/masculinization should include the following:

		a. psychosocial, voice use, voice health, and medical history b. clinical assessment of speech and voice including: 1.the client's subjective assessment 2.instrumental measurement 3.the clinician's subjective analysis 4.an assessment of potential for change 5.assistance with understanding therapeutic options 2.As there is evidence that behavioral changes (of pitch, inflection, resonance, etc.) may degrade over time, periodic re-evaluation is recommended following treatment with further clinical assistance as needed. *Voice and Communication Therapy* 1.Voice and communication therapy should be individualized based on each person's goals and identity, the risks and benefits of treatment options, and consideration of social and economic issues. 2.Rather than adopting a rigid and artificial set of voice and communication norms, it is recommended that clients be assisted to develop an individualized and context-specific set of norms based on communication patterns in their own social, cultural, work, and home environments. 3.It is clinically optimal to be able to offer both individual sessions and group treatment, with the proportion of time in each format depending on the client's therapeutic needs and goals. *Pitch-Elevating Surgery* 1.As there is no professional consensus regarding the effectiveness and risk-benefit ratio of pitch-elevating surgery, care should be taken to ensure that clients are fully informed of potential risks, postoperative care requirements, and possible outcomes (including decreased pitch). 2.Assessment by both a laryngologist and speech-language therapist is recommended prior to surgery. 3.Prior to surgery, the laryngologist should discuss after-care instructions with the patient and provide written after-care instructions. 4.Voice therapy should be offered following phonosurgery to help the patient adapt to and stabilize the new voice. *Outcome Evaluation* 1.Outcomes should be rigorously evaluated and documented. 2.At minimum, the baseline assessment should be repeated immediately following the end of therapy. Ideally, re-evaluation would take place at 6 months, 1 year, 5 years, and 10 years after treatment. 3.Evaluation should include client satisfaction with the treatment outcome and with the quality of care provided, as well as perceptual and objective measures of voice and communication change. 4.Informal or formal sharing of outcome data (with colleagues, at conferences, in publications, etc.) must occur only if the client has provided fully informed and voluntary written consent. *Research* 1.There is a paucity of data relating to speech feminization/masculinization. Further research in this area is eagerly anticipated. 2.To ensure that participation in research is voluntary, services should not be offered solely as part of a research protocol.
	ECDC (2018)	The ECDC guidance advocates for the development of an integrated national testing strategy or programme for HIV, HBV and HCV. Such integrated testing strategies or programmes should apply the six core testing principles, respect the individual needs of those tested and incorporate evidence-based interventions. Success in increasing the testing uptake should contribute considerably to the elimination of HIV and combat viral hepatitis as public health threat by 2030. *There are six overarching principles for HIV, HBV and HCV testing programmes in this context:* · An effective national testing strategy, including a monitoring and evaluation framework, is critical in responding to HIV, HBV and HCV infection. · Testing should be accessible, voluntary, confidential and contingent on informed consent. · Appropriate information should be available before and after testing. · Linkage to care is a critical part of an effective testing programme. · Normalising HIV, HBV and HCV testing in all healthcare settings; and · Those carrying out HIV, HBV and/or HCV testing should receive appropriate training and education. *Who to test?* The guidance identifies the following population groups suitable for targeted HIV, HBV and HCV testing due to higher risk of infection and suggest to offer tests to: · men who have sex with men (MSM) · trans* people · people who inject drugs (PWID) · migrants2 · household contacts of people diagnosed with HBV · homeless people · sex workers · people in prison · pregnant women · haemodialysis patients · people who have received blood products, organs or surgical interventions before adequate safety and quality regulations were enforced;

		and · sexual or injecting partners of people diagnosed with HIV, HBV and HCV. *Normalising testing* Making the testing offer a routine and with that making the process similar to those for other diagnostic test, helps to reduce stigma and increases testing uptake. The implementation of indicator condition-guided HIV testing provides a useful complement to targeted HIV testing of groups at higher risk. By providing a clinical rationale for testing, this strategy can also help normalise testing and reduce barriers to it, including issues around stigma among healthcare providers and patients alike. *Where to test?* The ECDC guidance outlines where, how and when to test for viral hepatitis and HIV by providing evidence-based options of testing strategies that are applicable to all healthcare settings, as well as testing strategies specifically for: · primary healthcare settings · hospital settings · other healthcare settings (e.g. STI clinics, pharmacies, prisons and some drug and harm reduction services) · community settings (including drug and harm reduction services); and · self-sampling and self-testing. *Frequency of testing* The suggested frequency of testing is3: · For those at risk of HIV infection – at least once a year and up to every three months depending on ongoing risk, sexual behaviour, history of sexually transmitted infections, use of pre- or post-exposure prophylaxis (PrEP, PEP) and local HIV prevalence or incidence. · For those at risk of HBV infection – test those at risk who have not had a complete course of HBV vaccinations based on vaccination history. Retesting up to every 6 to 12 months is only suggested if there is an ongoing risk for either unvaccinated people or vaccine non-responders. · For those at risk of HCV infection – consider testing all sex workers, people who inject drugs, trans* people, prisoners and migrants, and other populations at risk every 6 to 12 months depending on risk profile. *Testing strategies for all settings* *Focus* *I*n areas of intermediate (HBV/HCV) or high prevalence (HBV/HCV/HIV)[4]: · Consider identifying those who are unaware they are infected through geographically targeted routine testing. · Consider birth cohort or universal one-time testing as option to increase HCV testing coverage, taking into account local epidemiology, affordability and the availability of effective linkage-to-care pathways. *In addition*: · Test all patients diagnosed with either HIV, HBV and HCV infection for the other two viruses as per guidelines from the European AIDS Clinical Society (EACS)5 and European Association for the Study of the Liver (EASL)6,7. · As per the ECDC antenatal screening guidance8: offer pregnant women HBV and HIV tests during the first two trimesters of pregnancy. Offer an HCV test depending on the pregnant woman's risk profile. · Only for women at-risk: repeat HIV testing during pregnancy and HBV testing for those who decline HBV vaccination or are non-responders. · When a woman tests negative for HIV or HCV and has a partner at higher risk, facilitate testing of her partner. If the partner remains untested or risk factors are unknown, consider retesting the mother later in pregnancy. · Voluntary partner notification following a positive diagnosis helps to achieve earlier diagnosis and treatment of exposed (sexual) partners. *Testing in primary healthcare settings* Evidence shows that HIV, HBV and HCV testing in primary care (PHC) is acceptable and may effectively contribute to increase testing coverage and case detection. *Focus* Offer integrated testing to any person attending primary care if they: · identify as members of certain risk groups · present with clinical symptoms suggestive of one of three infections; or · show laboratory markers (including elevated liver enzymes) compatible with acute or chronic hepatitis or an HIV indicator condition, including a sexually transmitted infection. Rapid testing, dried blood spot testing and testing using venepuncture are all acceptable in primary care. · Consider offering all patients who were diagnosed with HBV, HCV or HIV a test for the other two viruses. *Considerations* · Although limited, evidence on general population testing in these settings is also encouraging, at least in intermediate- and high-prevalence regions and birth cohorts. · Available evidence suggests testing coverage in primary care settings is often suboptimal and caused by factors that discourage healthcare professionals from offering tests. Consider interventions to increase test offers, including educational interventions for healthcare staff and clinical decision-making tools. · For testing in PHC settings, appropriate clinical care pathways and referral systems need to be established to ensure better linkage to care for people newly diagnosed with HBV, HCV or HIV in primary care. *Testing in hospital settings* Testing for HIV, HBV and HCV in hospital settings is generally accepted by patients and staff and can contribute to better testing coverage and case detection among risk groups or people presenting with HIV indicator conditions. *Focus* Offer integrated testing to any person attending a hospital if they: · identify as members of certain risk groups · present with clinical symptoms suggestive of one of three infections; or · show laboratory markers (including elevated liver enzymes) compatible with acute or chronic hepatitis or an HIV indicator condition, including a sexually transmitted infection. Studies

		indicate that routine testing in emergency departments, including universal testing and integrated testing, is also acceptable to patients and staff in hospitals even though it is currently supported by limited evidence on its effectiveness. *Considerations* · Test all patients diagnosed with an HIV, HBV and HCV infection in hospital settings for the other two viruses, despite little current evidence on effectiveness. · Even though there is little evidence of the effectiveness of any specific intervention over any other, education and training programmes for healthcare staff, campaigns and clinical decision-making tools can support the offer and uptake of integrated testing strategies. *Testing in other healthcare settings* These settings include formal healthcare services (outside hospitals and primary care practices) such as STI, genito-urinary medicine, dermato-venereology and low-threshold clinics, pharmacies, antenatal, prison health, drug and harm reduction and tuberculosis services. *Focus* Based on available evidence for integrated testing in these specific settings: · Consider offering all patients diagnosed with an HBV, HCV or HIV infection a test for the other two viruses. · Ensure that people who are newly diagnosed with HBV, HCV or HIV are linked to care given that efficient testing strategies in these surroundings need appropriate pathways to care and effective referral systems. *Considerations* · Testing for HIV, HBV and HCV, including integrated testing, in such healthcare settings results in varying degrees of effectiveness regarding the increase of testing coverage and case detection. Limited evidence suggests that rapid diagnostic tests and dried blood spot tests are acceptable and may help to increase testing coverage in such sites. · Pharmacies generally offer HIV, HBV and HCV testing under the same quality standards that apply to healthcare settings despite very limited evidence currently on the effectiveness of this activity. · Harm reduction services offer and suggest HBV and HCV testing to everyone attending drug and harm reduction services and during their initial assessments. Repeat this offer in case of indicated ongoing risk. · Sites serving migrant populations can look into offering relevant testing to people who come from countries with intermediate (HCV) or high HIV, HBV and HCV prevalence. · Prison settings can look into offering HIV, HBV and HCV testing to all people in prison as per ECDC guidance on active case finding in prison settings given the higher prevalence of blood-borne viruses in many prison settings. See also the ECDC/European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) guidance on prevention and control of blood-borne viruses in prison settings9. STI/genito-urinary/dermato-venereology clinics can consider offering HIV testing to anyone seeking care regardless of symptoms or risk factors as part of the initial screening for STIs according to the International Union against Sexually Transmitted Infections' European guidelines. This includes offering HIV testing to those who: - have a high likelihood of exposure to HIV - are pregnant regardless of risk factors; or - voluntarily seek testing, especially if never tested before. Based on geographic prevalence and risk group, it may be appropriate to suggest HBV testing. *Testing in community settings* Community-based testing services refers to programmes and services that offer voluntary HIV and/or HBV, HCV testing outside formal healthcare facilities. They are designed to target specific population groups and clearly adapted and accessible to those communities. *Focus* There is a role for community-based testing to target groups at higher risk in any national testing strategy. They are acceptable and effective in increasing HIV, HBV and HCV testing coverage and case detection among these groups. Integrated testing and rapid testing may be offered for everyone accessing drug and harm reduction services in a community or outreach testing activities. Rapid testing in the community is acceptable and contributes to increased testing coverage when implemented in such settings. Options based on available evidence for integrated testing in these settings: · Linkage to care after HBV and HCV testing in community settings may currently be suboptimal, at least for certain risk groups. If testing in community settings is considered within a national testing scheme, clear pathways into care and other services have to be developed. This includes differentiated care pathways for the three infections and other services. · Testing services offered by lay providers help to increase testing opportunities, uptake and coverage. *Self-sampling and self-testing* Self-sampling and self-testing are additional options that give people the flexibility and privacy of performing an initial HIV, HBV and HCV test in their own homes or a place they consider convenient. To date, there is little scientific evidence on the effectiveness of self-sampling, especially relating to HCV and HBV, to reach any firm conclusions regarding inclusion in a national testing strategy. There is limited evidence that kits distributed to people attending an STI clinic may increase test coverage and frequency. *Focus* Self-sampling for HIV, HBV and HCV, including possible integrated sampling, is likely acceptable among those most at-risk and may contribute to increased testing coverage and case detection. Limited available evidence suggests that self-testing for HIV among men who have sex with men is acceptable and may increase testing coverage, frequency and case detection. Self-sampling kits can be effectively distributed through a variety of channels, such as pharmacies, healthcare settings, outreach activities and online platforms, but should be based on local circumstances and target populations *Considerations* To ensure effective linkage to care after self-sampling and/or self-testing as part of a testing strategy, clear pathways to care and other services need to be in place or

		developed, including differentiated care pathways for the three infections. *Contact tracing (includes voluntary partner notification)* Contact tracing, including partner notification, implies that people who may potentially have been exposed to an infection are informed of this possibility and are offered a test. This can also include other interventions depending on the specific infection. Partner notification is a voluntary process in which a trained provider asks a person diagnosed with HIV, HBV and HCV about details of their sexual partners, at-risk drug injecting partners and household contacts as indicated by the diagnosis and then offers to invite them for a test. The identity of the diagnosed person remains anonymous to the contact unless consent is given. *Focus* Even though there is currently limited evidence on the effectiveness of partner notification in increasing testing coverage and case detection, mainly related to HIV, it follows public health logic in response to other communicable diseases to offer voluntary anonymous partner notification to every patient with a newly confirmed diagnosis. There are various strategies to implement partner notification, including passive notification, assisted anonymous notification using a web-based platform and assisted notification with the direct involvement of the service provider. *Considerations* Current implementation of partner notification processes appears to be suboptimal across Europe. While the success of interventions to increase the coverage of partner notification may depend on local factors, including organisational and legal circumstances, educational interventions targeting healthcare workers may prove to be beneficial. *Monitoring integrated national testing strategies or programmes for HBV, HCV and HIV* Monitoring and evaluation is an essential component of any effective testing programme. While strategic information should guide the design of testing initiatives, monitoring and evaluation data permit continuous reevaluation of targets as well as assessment of programme effectiveness, efficiency and impact. Such data can prove invaluable in planning improvements
	Gilligan et al. (2017)	1. Core communication skills 1.1. Before each conversation, clinicians should review the patient's medical information, establish goals for the conversation, and anticipate the needs and responses of the patient and family. 1.2. At the beginning of conversations with patients, clinicians should explore the patient's understanding of their disease and collaboratively set an agenda with the patient after inquiring what the patient and family wish to address and explaining what the clinician wishes to address. 1.3. During patient visits, clinicians should engage in behaviors that actively foster trust, confidence in the clinician, and collaboration. 1.4. Clinicians should provide information that is timely and oriented to the patient's concerns and preferences for information. After providing information, clinicians should check for patient understanding and document important discussions in the medical record. 1.5. When patients display emotion through verbal or nonverbal behavior, clinicians should respond empathically. 2. Discussing goals of care and prognosis 2.1. Clinicians should provide diagnostic and prognostic information that is tailored to the patient's needs and that provides hope and reassurance without misleading the patient. 2.2. Clinicians should reassess a patient's goals, priorities, and desire for information whenever a significant change in the patient's care is being considered. 2.3. Clinicians should provide information in simple and direct terms. 2.4. When providing bad news, clinicians should take additional steps to address the needs and responses of patients. 3. Discussing treatment options and clinical trials 3.1. Before discussing specific treatment options with the patient, clinicians should clarify the goals of treatment (cure v prolongation of survival v improved quality of life) so that the patient understands likely outcomes and can relate the goals of treatment to their goals of care. 3.2. When reviewing treatment options with patients, clinicians should provide information about the potential benefits and burdens of any treatment (proportionality) and check the patient's understanding of these benefits and burdens. 3.3. Clinicians should discuss treatment options in a way that preserves patient hope, promotes autonomy, and facilitates understanding. 3.4. Clinicians should make patients aware of all treatment options, including clinical trials and a sole focus on palliative care. When appropriate, clinicians should discuss the option of initiating palliative care simultaneously with other treatment modalities. If clinical trials are available, clinicians should start treatment discussions with standard treatments available off trial and then move to a discussion of applicable clinical trials if the patient is interested. 4. Discussing end-of-life care 4.1. Clinicians should use an organized framework to guide the bidirectional communication about end-of-life care with patients and families. 4.2. Clinicians should initiate conversations about patients' end-of-life preferences early in the course of incurable illness and readdress this topic periodically based on clinical events or

		patient preferences. 4.3. Clinicians should explore how a patient's culture, religion, or spiritual belief system affects their end-of-life decision making or care preferences. 4.4. Clinicians should recognize and respond empathically to grief and loss among patients, families, and themselves. Clinicians should refer patients and families to psychosocial team members (eg, social workers, counselors, psychologists, psychiatrists, and clergy) when appropriate. 4.5. Clinicians should identify and suggest local resources to provide robust support to patients, families, and loved ones transitioning to end-of-life care. 5. Using communication to facilitate family involvement in care 5.1. Clinicians should suggest family and/or caregiver involvement in discussions (with patient consent) early in the course of the illness for support and discussion about goals of care. 5.2. Determine if a formal family meeting in a hospital or outpatient setting is indicated at important junctures in care. When possible, ensure that patients, their designated surrogates, and desired medical professionals are present. 6. Communicating effectively when there are barriers to communication 6.1. For families who do not share a common language with the clinician, use a medical interpreter rather than a family interpreter. 6.2. For patients with low health literacy, focus on the most important points, use plain language, and check frequently for understanding. 6.3. For patients with low health numeracy, use pictographs or other visual aids when available, and describe absolute risk rather than relative risk. 7. Discussing cost of care 7. Clinicians should explore whether cost of care is a concern for patients with cancer. 8. Meeting the needs of underserved populations 8.1. Enter clinical encounters with a sense of curiosity, aware that any patient and family, regardless of their background, may have beliefs, experiences, understandings, and expectations that are different from the clinician's. 8.2. Avoid assumptions about sexual orientation and gender identity and use nonjudgmental language when discussing sexuality and sexual behavior. 8.3. Remain aware that members of underserved or marginalized populations have an increased likelihood of having had negative past health care experiences, including feeling disrespected, alienated, or unsafe. 9. Clinician training in communication skills 9.1. Communication skills training should be based on sound educational principles and include and emphasize skills practice and experiential learning using role-play scenarios, direct observation of patient encounters, and other validated techniques. 9.2. For communication skills training to be most effective, it should foster practitioner self-awareness and situational awareness related to emotions, attitudes, and underlying beliefs that may affect communication as well as awareness of implicit biases that may affect decision making. 9.3. Facilitators of communication skills training should have sufficient training and experience to effectively model and teach the desired communication skills and facilitate experiential learning exercises.
5	Hembree et al. (2017)	*1.0 Evaluation of youth and adults* 1.1. We advise that only trained mental health professionals (MHPs) {and/or trained physicians**}** who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. 1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. 1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. 1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence.

		1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. *2.0 Treatment of adolescents* 2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. 2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty. 2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. 2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years. 2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. 2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment. *3.0 Hormonal therapy for transgender adults* 3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. 3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. 3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. 3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. *4.0 Adverse outcome prevention and long-term care* 4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. 4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. 4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. 4.4. We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. 4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females. 4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. 4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. *5.0 Surgery for sex reassignment and gender confirmation* 5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. 5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. 5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. 5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes.

		5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. 5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement.
	IAPHCCO (2015)	*Optimizing the HIV care environment* 1. Laws that criminalize the conduct of or exert punitive legal measures against MSM, transgender individuals, substance users, and sex workers are not recommended and should be repealed where they have been enacted. 2. Laws that criminalize the conduct of PLHIV based on perceived exposure to HIV, and without any evidence of intent to do harm, are not recommended and should be repealed where they have been enacted. 3. HIV-related restrictions on entry, stay, and residence in any country for PLHIV are not recommended and should be repealed where they have been enacted. 4. Strategies to monitor for and eliminate stigma and discrimination based on race, ethnicity, gender, age, sexual orientation, and/or behavior in all settings, but particularly in health care settings, using standardized measures and evidence-based approaches, are recommended. 5. Proactive steps are recommended to identify and manage clinical mental health disorders (eg, anxiety, depression, and traumatic stress) and/or mental health issues related to HIV diagnosis, disclosure of HIV status, and/or HIV treatment. 6. Enabling PLHIV to take responsibility for their care (eg, self-management, user-driven care) is recommended. 7. Shifting and sharing HIV testing, dispensing of ART, and other appropriate tasks among professional and paraprofessional health worker cadres is recommended. 7a. Use of lay health workers to provide pretest education and testing and to enhance PLHIV engagement in HIV care is recommended. 7b. Task shifting/sharing from physicians to appropriately trained health care providers, including nurses and associate clinicians, is recommended for ART initiation and maintenance. 8. Community engagement in every step across the HIV care continuum is recommended. *Increasing HIV testing coverage and linkage to care* 9. Routinely offering opt-out HIV testing to all individuals who present at health facilities is recommended. 10. Community-based HIV testing is recommended to reach those who are less likely to attend facility-based HIV testing. 11. Confidential, voluntary HIV testing in large workplace and institutional settings (military, police, mining/trucking companies, and educational venues) should be considered. (B III) 12. HIV self-testing is recommended with the provision of guidance about the proper method for administering the test and direction on what to do once the results have been obtained. 13. Use of epidemiological data and network analyses to identify individuals at risk of HIV infection for HIV testing is recommended. 14. The offer of HIV testing to partners of newly diagnosed individuals is recommended. 15. Immediate referral to HIV care is recommended following an HIV-positive diagnosis to improve linkage to ART. 16. For high-risk individuals who test HIV negative, offering PrEP is recommended in addition to the provision of free condoms, education about risk reduction strategies, PEP, and voluntary medical male circumcision. 17. Use of case managers and patient navigators to increase linkage to care is recommended. *Increasing HIV treatment coverage* 18. The immediate offer of ART after HIV diagnosis, irrespective of CD4 count or clinical stage, is recommended. 19. First-line ARV regimens with the highest levels of efficacy, lowest adverse event profiles, and delivered in QD fixed-dose combinations are recommended. 20. Viral load testing at least every 6 months is recommended as the preferred tool for monitoring ART response. 21. HIV drug resistance testing is recommended at entry into care or prior to ART initiation and when virologic failure is confirmed. 21a. Where routine access to HIV drug resistance testing is restricted, population-based surveillance is recommended. 22. Community-located ART distribution is recommended. 22a. The use of community-based pharmacies should be considered. *Increasing retention in care, ART adherence, and viral suppression* 23. Systematic monitoring of retention in HIV care is recommended for all patients. 23a. Retention in HIV care should be considered as a quality indicator. 23b. Measuring retention in HIV care using electronic health record and other health system data is recommended. 23c. Use of clinic databases/surveillance systems for HIV clinical monitoring and population-level tracking is recommended.

		24. Routine ART adherence monitoring is recommended in all patients. 24a. Viral suppression is recommended as the primary adherence monitoring metric. 24b. Routine collection of self-reported adherence data from patients is recommended. 24c. Pharmacy refill data are recommended for adherence monitoring. 25. Information and communication technologies aimed at supporting patient self-care are recommended. 25a. Mobile health technology using weekly interactive components (eg, 2-way SMS) is recommended. 25b. Alarm devices are recommended as reminders for PLHIV with memory impairment. 26. Patient education about and offering support for medication adherence and keeping clinic appointments are recommended. 26a. Pillbox organizers are recommended, particularly for HIV-infected adults with lifestyle-related barriers to adherence. 27. Neither directly administered nor directly observed ART is recommended for routine clinical care settings. 27a.DirectlyadministeredARTis recommended for people who inject drugs and released prisoners at high risk of ARTnon adherence. 28. Proactive engagement and reengagement of patients who miss clinic appointments and/or are lost to follow-up, including intensive outreach for those not engaged in care within 1 month of a new HIV diagnosis, is recommended. 28a. Case management to retain PLHIV in care and to locate and reengage patients lost to follow-up is recommended. (B II) 28b. Transportation support for PLHIV to attend their clinic visits is recommended. *Adolescents* 29. Removing adult-assisted consent to HIV testing and counseling is recommended for minor adolescents with the capacity to consent. (B II) 30. Adolescent-centered services are recommended in both clinical and community-based settings. 31. Informing an adolescent of his/her HIV-positive diagnosis is recommended as soon after diagnosis as feasible. (B II) 32. A transition plan between pediatric and adult HIV care is recommended. *Metrics for and monitoring of the HIV care continuum* 33. A standardized method should be used to estimate the total number of PLHIV (diagnosed and undiagnosed) within a geographi csetting. 34. The estimated number of PLHIV in the geographic setting should be the overall denominator for the HIV care continuum. 35. Collection of a minimum set of 5 data elements should be considered to populate the HIV care continuum. Estimated number of PLHIV Number and proportion of PLHIV who are diagnosed as having HIV Number and proportion of PLHIV who are linked to care (optional) Number and proportion of PLHIV on ART Number and proportion of PLHIV on ART who are virally suppressed 36. Where possible, jurisdictions should consider longitudinal cohort measurement of HIV service utilization and treatment outcomes to identify the means to maximize viral suppression through ensuring early access to ART and retention in care.
7	Ralph et al. (2010)	*Recommendation for Penile Fracture* Imaging (cavernosography, US, or MRI) can be used for localization of the injury, while retrograde urethrogram (pre-/perioperative) can be performed if there is a suspicion of a urethral injury. The ultimate decision for surgery is based on clinical findings and once diagnosed, there is no indication for conservative management. *Recommendation for Skin Loss Injuries* There is evidence to support surgical replacement of shaft skin with either split, mesh, or full thickness skin. *Recommendation for Penile Amputation* Critical warm and cold ischemia time is unknown. Surgical reattachment is therefore a clinical decision and is best performed by an experienced microsurgeon. Psychological evaluation should be offered to patients who self-mutilate. If re-implantation fails or is impossible, patients should be referred for phalloplasty at an appropriate time interval. *Definition of Gender Identity Disorder/ Transexualism* The desire for at least 2 years, to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone therapy. *Male-to-Female Genital Surgery* Bilateral orchiectomy, amputation of the corpora cavernosa, creation of a neovaginal cavity that is lined by hairless skin, the formation of a sensate neoclitoris, and an aesthetic vulval appearance are the aims of genital surgery. The outcome may be achieved in one or two stages with satisfaction rates of 80% expected. *Female-to-Male Genital Surgery*

		Breast reduction, oophorectomy, hysterectomy, and vaginectomy should be offered to all patients. There are many phalloplasty techniques involving local or free flaps and mircrosurgery. Patients should be warned that multiple stages are often needed with high urethral and prosthetic complication rates. However, a universal satisfaction rate of 80% should be expected. Metoidioplasty can be offered to those who wish to stand to void but do not want sexual intercourse. *Penile Augmentation – Indications* A stretched penile length of <7cm should be considered as a micropenis with many surgical techniques being recommended. The indications for augmentation in men with a normal-sized penis cannot be drawn from the literature *Penile Augmentation – Surgical Techniques* There are many lengthening techniques described with variable success rates. The complications may be significant. Stretching devices may be an alternative treatment option. All operative methods of girth enhancement have no proven efficacy outcome data. Liquid silicone injection should be discouraged. Psychological assessment should proceed any surgical approach
	Strang et al. (2016)	*Emergency intakes:* If the adolescent presents in a state of emergency, as some gender dysphoria (GD) referrals do, then as in any assessment, the first priority is risk reduction/safety. Hospitalization may be necessary in extreme cases to prevent self-harm/mutilation, though psychiatric hospital units are often not equipped to work with gender dysphoric adolescents with autism spectrum disorders (ASD), and so outside consultation to the unit may be necessary. Ultimately, engaging a therapist with training (or consultation support) in both ASD and gender nonconformity/GD may be a critical step; helping a patient understand that relief is coming and that their gender-needs will be addressed may reduce safety risks, and support further assessment. *ASD assessment:* When an ASD diagnosis is suspected, it is important for an autism specialist to confirm the diagnosis, if a diagnosis has not been established. Whenever possible, a neuropsychological/autism evaluation should be conducted to evaluate the impact of ASD on an adolescent's ability to understand and report GD symptoms as well as engage in therapy/treatments. Evaluations should include assessment of general cognitive skills, executive function skills (impulse control, flexibility, planning, future thinking), communication skills, emotional functioning, self-awareness/social cognition, and capacity for self-advocacy. Knowledge of the young person's capacities will inform the GD diagnosis process (i.e., how to best obtain clinical/diagnostic information and understand that information), as well as deciding on clinical treatment options (i.e., the ability to understand treatments, comply with treatments, consider a range of gender possibilities vs. concrete/black-and-white thinking). *Gender-related assessment:* When gender issues are reported/suspected in an adolescent with ASD, a structured interview should be used to assess for gender dysphoria, including dysphoria over time, intensity of dysphoria, and its pervasiveness. Whenever possible, it is important to obtain additional report from other sources (e.g., parents), as communication, self-awareness, and self-advocacy skills may be vulnerable in adolescents with ASD. It is difficult to separate the assessment and treatment of many of these individuals, because assessment continues throughout the treatment process as the person may develop increased understanding of themselves and increased ability to express their wants and needs. Therefore, gender-related diagnostics may take more time. For some individuals, however, GD diagnosis is immediately clear, such as when the dysphoria has been present for an extended period, the young person is already presenting as a different gender, or when the level of urgency about gender transition is extreme. *Treatment checklist (psychosocial and medical).* Establish appropriate clinical team, ideally a clinician trained in both autism spectrum disorders (ASD) and gender nonconformity/ gender dysphoria (GNC/GD), or clinicians collaborating from each specialty. Address and assess intensity of gender feelings/urgency throughout the treatment process, as assessment often continues during treatment, informing and shaping the goals of the treatment. Key clinical questions: a. Is the GD clear, urgent, pervasive, and persistent over time (i.e., meeting full diagnostic criteria for GD)? If yes, consultation with medical transition services may be indicated (see "If medical transition is indicated" below). b. Does the GD increase or decrease with intervention (e.g., as adolescent develops increased social/self-awareness, executive function flexibility and big picture thinking skills, communication/self-advocacy skills)? Provide psycho-education about and explore the possibility of a range of gender outcomes (e.g., gender spectrum, incorporating aspects of a different gender without full gender transition, etc.) This may require specific approaches targeting ASD related deficits in cognitive flexibility (i.e., reducing all or nothing/black and white thinking). Provide structure, as necessary, for gender exploration, supporting the adolescent's ability to explore gender transition, including clothing, name, pronouns, etc. Parents may need to assume a central role in helping facilitate an individual's exploration of their gender when ASD-related weaknesses in daily living skills, planning and self-advocacy interfere with that

		exploration. Such family support may include reminding a young person of their gender exploration therapy goals during the week, helping a young person to obtain appropriate clothing to try on, and so forth. Over the course of treatment, assess for signs that the adolescent's experience of GNC/GD is caused by comorbidities or symptoms of ASD (e.g., ASD preoccupations, misinterpreting sexual orientation for gender, etc.) If it becomes clear that a wish to transition is caused by a comorbidity or symptoms of ASD, explore alternative solutions to gender transition. If medical transition is indicated during the process, ensure that a pediatric endocrinologist (or similar medical specialist) trained in GD is engaged in the treatment to discuss risks/benefits of pubertal blockade and/or cross sex hormones. The endocrinologist/medical specialist and other treatment providers (e.g., autism specialist) should collaborate around diagnostics and treatments. If medical treatments begin, provide concrete psycho-education about treatment side effects, risks and benefits and ensure that these issues are understood by the adolescent with concurrent GD and ASD. Consider the accessibility and appropriateness of adjunct gender and/or ASD-related supports/services. Provide support, coaching, and vetting as needed. For example, an LGBT youth group leader may require some coaching in how to welcome and engage a person with ASD, and an autism skills group provider may require support in how to work with a GD/gender nonconforming adolescent.
	T'Sjoen et al. (2020)	1.We advise that HCPs when working with trans people recognize the diversity of genders, including male, female, and nonbinary individuals. 2. We advise that HCPs when working with trans people openly ask for the individual gender experience of the person seeking treatment, including which pronouns and name they like to be addressed with, and recognize this may change in the future. 3. We advise that HCPs when working with trans people critically reflect upon discriminatory factors influencing both access to and outcomes of gender-related health-care services and make the necessary changes to accommodate all trans individuals. 4. We advise that HCPs when working with trans people should critically reflect on their own possible prejudices, ethics, and power positions. 5. We advise that HCPs when working with adult trans people should explain the result of the clinical assessment with the aim of a shared understanding and shared responsibility. 6. We advise that HCPs assessing gender diverse children and adolescents support the exploration and expression of the youth's experienced gender and help to reduce experienced barriers for those seeking care. 7. We advise that HCPs assessing gender diverse children and adolescents take a developmental approach that includes that gender-related developmental pathways may be more open to change in prepubescent gender diverse children than in pubescent gender diverse adolescents and adults. 8. We advise that HCPs assessing gender diverse children and adolescents assess resilience and vulnerabilities and treat (or refer for treatment) possible mental health problems. 9. We advise that HCPs assessing gender diverse children and adolescents support parents and/or legal guardian and school and other important social networks (when possible) to provide a safe and accepting home and school environment. 10. For prepubescent gender diverse children who desire to live in a role consistent with their experienced gender identity, we advise the HCPs advise that parents and the social environment consider social transitioning of the child after discussing the pros and the cons and while providing continuous psychological support. 11. For pubertal gender diverse adolescents, we advise that HCPs inform and explore all nonmedical and medical options, including the effect that GAMIs (puberty blockers, hormones as well as surgical) may have on sexuality and fertility and if indicated, facilitate GAMIs. 12. In countries requiring an assessment process including a clinical diagnosis to access GAMI, we advise that HCPs assessing trans adolescents for GAMI have the expertise in reaching the required diagnosis for their health service 13. We advise that HCPs working with trans people should inform trans adults seeking GAMI of its effect and assess the capacity of the individual to reach an informed consent regarding GAMI. 14. We advise that, in view of the strong evidence regarding the high levels of mental health problems in adults presenting at trans health services, particularly in those not on hormone treatment, HCPs whose role is informing and assessing the capacity to consent for GAMI in trans people wishing these interventions should have expertise in mental health to be able to identify those requiring further support from mental health professionals to allow for the best possible outcome of GAMI. 15. We advise that HCPs whose role is informing and assessing the capacity to consent for GAMI in trans people wishing these interventions should explore resilience and social support, in view of its association with health-related quality of life and psychological well-being. 16. We advise that HCPs whose role is informing and assessing the capacity to consent for GAMI in trans people wishing these interventions should inform clients about the effect that GAMIs (hormones and surgical) may have on sexual health and fertility. 17. In countries requiring an assessment process including a clinical diagnosis to access GAMI, we advise that HCPs assessing trans adults for GAMI have the expertise in reaching the required diagnosis for their health service. 18. We advise initiating pubertal hormone suppression in trans adolescents, when gender incongruence or nonconformity is assessed, interfering psychosocial difficulties are addressed if possible, and after they show their first pubertal changes (Tanner stage G2) and when they have sufficient capacity to give informed consent.

		19. We advise in adolescents desiring masculinizing hormone treatment, when they have sufficient capacity to give informed consent, puberty induction with testosterone, often using a gradually increasing dose schedule. 20. We advise that before initiation of gonadotropin-releasing hormone analogs (GnRHa) or progestogen and/or testosterone, the hormone-prescribing physician should screen for conditions that may worsen with the start of treatment. 21. If masculinization is desired, we advise testosterone therapy with monitoring of serum sex steroid levels and signs of virilization. 22. We advise the hormone-prescribing physician discusses the effects and possible adverse health effects of GnRHa, progestogen, and/or testosterone treatment, including fertility preservation options, based on the person's goals before any hormonal intervention. 23. We advise informing trans subjects on the expected changes upon GnRHa, progestogen, and/or testosterone initiation on its effect on body satisfaction and on sexual function (desire and activity) and considering the role that factors such as relationship status and possible surgical interventions will play. 24. We advise initiating pubertal hormone suppression in trans adolescents, when gender incongruence or nonconformity is assessed, interfering psychosocial difficulties are addressed if possible, and after they show their first pubertal changes (Tanner stage G2) and when they have sufficient capacity to give informed consent. 25. We advise in adolescents desiring feminizing hormone treatment, when they have sufficient capacity to give informed consent, puberty induction with 17beta-estradiol, often using a gradually increasing dose schedule. 26. We advise that before initiation of GnRHa or antiandrogen and/or estrogen treatment, the hormone-prescribing physician needs to screen for conditions that may worsen with the start of treatment. 27. If feminization is desired, we advise estrogens and/or antiandrogen therapy with monitoring of serum sex steroid levels and signs of feminization. 28. We advise the hormone-prescribing physician discusses the effects and possible adverse health effects of GnRHa, antiandrogen, and/or estrogen treatment, including fertility preservation options and consequences for genital surgery, based on the person's goals before any hormonal intervention. 29. We advise informing trans clients on the expected changes upon GnRHa, estrogen, and/or anti-androgen initiation and its effect on body satisfaction, sexual desire and activity and considering the role factors such as relationship status and possible surgical interventions can play 30. We advise HCPs should be aware of potential sexual problems during all surgical phases of treatment. 31. We advise that regardless of surgical pathways, HCPs should be aware of diversity in sexual practices in trans people. 32. We advise that surgeons performing GAS collaborate with sexologists with knowledge and experience with trans people, if available.
	WHO (2011)	*Recommendations on human rights and non-discrimination in health-care settings* 1. Legislators and other government authorities should establish antidiscrimination and protective laws, derived from international human rights standards, in order to eliminate discrimination and violence faced by MSM and transgender people, and reduce their vulnerability to infection with HIV, and the impacts of HIV and AIDS. 2. Health services should be made inclusive of MSM and transgender people, based on the principles of medical ethics and the right to health. *Recommendations on HIV prevention, care and treatment* *Prevention of sexual transmission* 3. Using condoms consistently during anal intercourse is strongly recommended for MSM and transgender people over not using condoms. 4. Using condoms consistently is strongly recommended over serosorting for HIV-negative MSM and transgender people. Serosorting is suggested over not using condoms by HIV-negative MSM and transgender people under specific circumstances as a harm reduction strategy. 5. Not offering adult male circumcision to MSM and transgender people for the prevention of HIV and STI is suggested over offering it 6. Offering HIV testing and counselling to MSM and transgender people is strongly recommended over not offering this intervention 7. Offering community-based HIV testing and counselling linked to care and treatment to MSM and transgender people is strongly recommended over not offering such programmes *Behavioural interventions, information, education, communication* 8. Implementing individual-level behavioural interventions for the prevention of HIV and STIs among MSM and transgender people is suggested over not implementing such interventions. 9. Implementing community-level behavioural interventions for the prevention of HIV and STIs among MSM and transgender people is suggested over not implementing such interventions. 10. Offering targeted internet-based information to decrease risky sexual behaviours and increase uptake of HIV testing and counselling among MSM and transgender people is suggested over not offering such information. 11. Using social marketing strategies to increase the uptake of HIV/STI testing and counselling and HIV services among MSM and transgender people is suggested over not using such

		strategies. 12. Implementing sex venue-based outreach strategies to decrease risky sexual behaviour and increase uptake of HIV testing and counselling among MSM and transgender people is suggested over not implementing such strategies. Substance use and prevention of bloodborne infections 13. MSM and transgender people with harmful alcohol or other substance use should have access to evidence-based brief psychosocial interventions involving assessment, specific feedback and advice. 14. MSM and transgender people who inject drugs should have access to needle and syringe programmes and opioid substitution therapy. 15. Transgender people who inject substances for gender enhancement should use sterile injecting equipment and practise safe injecting behaviours to reduce the risk of infection with bloodborne pathogens such as HIV, hepatitis B and hepatitis C. *HIV care and treatment* 16. MSM and transgender people living with HIV should have the same access to ART as other populations. ART should be initiated at CD4 counts of ≤350 cells/mm3 (and for those in WHO clinical stage 3 or 4 if CD4 testing is not available). Access should also include management of opportunistic infections, co-morbidities and treatment failure. 17. MSM and transgender people living with HIV should have access to essential interventions to prevent illness and HIV transmission including, but not limited to, care and support and antiretroviral therapy. *Recommendations on prevention and care of other sexually transmitted infections* 18. MSM and transgender people with symptomatic STIs should seek and be offered syndromic management and treatment. 19. Offering periodic testing for asymptomatic urethral and rectal N. gonorrhoeae and C. trachomatis infections using NAAT is suggested over not offering such testing for MSM and transgender people. Not offering periodic testing for asymptomatic urethral and rectal N. gonorrhoeae infections using culture is suggested over offering such testing for MSM and transgender people. 20. Offering periodic serological testing for asymptomatic syphilis infection to MSM and transgender people is strongly recommended over not offering such screening 21. MSM and transgender people should be included in catch-up HBV immunization strategies in settings where infant immunization has not reached full coverage
	WHO (2012)	1: In countries where HIV transmission occurs among serodiscordant couples, where discordant couples can be identified and where additional HIV prevention choices for them are needed, daily oral PrEP (specifically tenofovir or the combination of tenofovir and emtricitabine) may be considered as a possible additional intervention for the uninfected partner. 2: In countries where HIV transmission occurs among men and transgender women who have sex with men and additional HIV prevention choices for them are needed, daily oral PrEP (specifically the combination of tenofovir and emtricitabine) may be considered as a possible additional intervention.
	WHO (2016)	*HIV prevention* 1 The correct and consistent use of condoms with condom-compatible lubricants is recommended for all key populations to prevent sexual transmission of HIV and sexually transmitted infections (STIs). 2 Oral pre-exposure prophylaxis (PrEP) containing tenofovir disproxil fumerate (TDF) should be offered as an additional prevention choice for key populations at substantial risk of HIV infection as part of combination HIV prevention approaches. 3 Post-exposure prophylaxis (PEP) should be available to all eligible people from key populations on a voluntary basis after possible exposure to HIV. 4 Voluntary medical male circumcision (VMMC) is recommended as an additional important strategy for the prevention of heterosexually acquired HIV infection in men, particularly in settings with hyperendemic and generalized HIV epidemics and low prevalence of male circumcision. *Harm reduction* 5 All people from key populations who inject drugs should have access to sterile injecting equipment through needle and syringe programmes. 6 All people from key populations who are dependent on opioids should be offered and have access to opioid substitution therapy in keeping with WHO guidance. 7 All people from key populations with harmful alcohol or other substance use should have access to evidence-based interventions, including brief psychosocial interventions involving assessment, specific feedback and advice. 8 People likely to witness an opioid overdose should have access to naloxone and be instructed in its use for emergency management of suspected opioid overdose. *HIV testing and counselling (HTC)* 9 Voluntary HTC should be routinely offered to all key populations both in the community and in clinical settings. Community-based HIV testing and counselling for key populations, linked to prevention, care and treatment services, is recommended, in addition to provider-initiated testing and counselling. *HIV treatment and care*

		10 Key populations living with HIV should have the same access to antiretroviral therapy (ART) and to ART management as other populations. 11 All pregnant women from key populations should have the same access to services for prevention of mother-to-child transmission of HIV (PMTCT) and follow the same recommendations as women in other populations. *Prevention and management of coinfections and co-morbidities* 12 Key populations should have the same access to tuberculosis prevention, screening and treatment services as other populations at risk of or living with HIV. 13 Key populations should have the same access to hepatitis B and C prevention, screening and treatment services as other populations at risk of or living with HIV. 14 Routine screening and management of mental health disorders (depression and psychosocial stress) should be provided for people from key populations living with HIV in order to optimize health outcomes and improve their adherence to ART. Management can range from co-counselling for HIV and depression to appropriate medical therapies. *Sexual and reproductive health* 15 Screening, diagnosis and treatment of sexually transmitted infections should be offered routinely as part of comprehensive HIV prevention and care for key populations. 16 People from key populations, including those living with HIV, should be able to experience full, pleasurable sex lives and have access to a range of reproductive options. 17 Abortion laws and services should protect the health and human rights of all women, including those from key populations. 18 It is important to offer cervical cancer screening to all women from key populations, as indicated in the WHO 2013 cervical cancer screening guidelines. 19 It is important that all women from key populations have the same support and access to services related to conception and pregnancy care, as indicated by WHO guidelines, as women from other populations. *Critical enablers* 1 Laws, policies and practices should be reviewed and revised where necessary, and countries should work towards decriminalization of behaviours such as drug use/injecting, sex work, same-sex activity and non-conforming gender identity and toward elimination of the unjust application of civil law and regulations against people who use/inject drugs, sex workers, men who have sex with men and transgender people. 2 Countries should work towards implementing and enforcing antidiscrimination and protective laws, derived from human rights standards, to eliminate stigma, discrimination and violence against people from key populations. 3 Health services should be made available, accessible and acceptable to key populations, based on the principles of medical ethics, avoidance of stigma, non-discrimination and the right to health. 4 Programmes should work toward implementing a package of interventions to enhance community empowerment among key populations. 5 Violence against people from key populations should be prevented and addressed in partnership with key population led organizations. All violence against people from key populations should be monitored and reported, and redress mechanisms should be established to provide justice

Key: {text}, appeared in corrected version; AIDS acquired immune deficiency syndrome; ART, antiretroviral therapy; CD4, T-cell; ECDC, European Centre for Disease Prevention and Control; FtM, female to male; GAMI, gender affirming medical intervention; GAS, gender affirming surgery; HBV, hepatitis B virus; HCV, hepatitis C virus; HCP, health care professional; HIV, human immunodeficiency virus, MSM, men who have sex with men; MtF, male to female; PWID people who inject drugs; STI, sexually transmitted infection; WHO, World Health Organization.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-9
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	10, 12
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	10-11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	W1 (Suppl)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10-12
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	N/A (in AGREE)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	AGREE
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Within AGREE
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	None
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	14 & Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	14-19, Table 1, W3,W4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	19-24, Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	19-24
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	None
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	24-25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	25-29
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	30

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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