A PROTOCOL TO DEVELOP CLINICAL GUIDELINES FOR INCLUSION-BODY MYOSITIS

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ABSTRACT: *Introduction:* Inclusion-body myositis (IBM) is a late-onset idiopathic inflammatory myopathy associated with selective and progressive muscle weakness and atrophy. Current clinical management of IBM is largely supportive due to its uncertain etiology and lack of effective treatment. Establishing a consensus of opinion on questions relating to diagnosis and management of IBM is expected to help reduce inconsistencies in the care and resources allocated to those living with this condition. *Methods:* A protocol has been developed to produce best practice clinical guidelines for IBM based on a combination of published research and expert consensus. *Conclusions:* In this study we describe the proposed protocol for developing methods for producing robust and transparent clinical guidance on aspects of diagnosis, drug treatment, physical and practical management, respiration, nutrition and cardiac management, psychosocial management, and multidisciplinary care.

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Inclusion-body myositis (IBM) is a late-onset and progressive idiopathic inflammatory myopathy that is currently estimated to affect up to 14.9 people per million and 51.3 per million population aged >50 years of age.[1] IBM has preferential involvement of certain muscle groups, including the quadriceps and extrinsic finger flexors.[2,3] As a consequence of muscle weakness, many people with IBM experience difficulties with managing everyday activities.[4,5] A subgroup of patients also experience dysphagia.[6] Due to its uncertain etiology and lack of definitive treatment,[7] there continues to be variation in both the diagnosis and management of IBM, even among specialists. Agreed-upon diagnostic and management guidelines could optimize and streamline the care given to IBM patients; they could also form the basis for national and international standards of care.

The rarity of IBM, combined with limited access to specialists, means that much of the management of patients with the disease may be delivered by health professionals who are unfamiliar with the condition. Access to clinical guidelines for IBM could be invaluable for non-specialists. It was for such reasons that a meeting of specialist clinicians at the 188th European Neuromuscular Center (ENMC) International Workshop agreed on the need and scope for establishing clinical guidelines in IBM.[8]

Currently, there are neuromuscular disease-specific guidelines available for conditions including Duchenne muscular dystrophy,[9] spinal muscular atrophy,[10,11] amyotrophic lateral sclerosis,[11,12] and facioscapulohumeral muscular dystrophy.[13] Also, various organizations promote and author guidelines, such as the American Academy of Neurology (AAN), the Scottish Intercollegiate Guidelines Network, and the National Institute of Clinical Excellence (NICE) in the UK. For many, guideline construction starts with a search of the literature, followed by evidence ranking and formation of recommendations that are graded accordingly. This approach assumes the existence of an evidence base that will cover the issues the clinical guidelines aim to address. Furthermore, there are a number of

Abbreviations: AAN, American Academy of Neurology; CASP, Critical Appraisal Skills Programme; ENMC, European Neuromuscular Centre; GDG, Guideline Development Group; h-IBM, hereditary inclusion-body myopathy; IBM, inclusion-body myositis; ICTRP, International Clinical Trials Registry Platform; NICE, National Institute for Health and Care Excellence; PICO, Patient/Population, Intervention, Comparison and Outcome; RCT, randomized, controlled trial; WHO, World Health Organization

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Key words: diagnosis; guidelines; IBM; management; protocol

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different classification systems for evidence ranking. Hierarchical ranking of the knowledge base often categorizes expert opinion separately within such classification systems, placing a bias in favor of randomized, controlled trials (RCTs) and meta-analyses, even though these approaches may be inappropriate to address certain clinical practice questions. As a result of such hierarchical ranking, guideline recommendations may appear to be weakly supported when they are based on expert opinion only. In developing a guideline protocol, we considered these challenges and decided to adopt a mixed methods approach to constructing clinical guidelines for IBM.

As with systematic reviews, preparing guidelines involves many judgments.[14] Guideline construction is not standardized, and the methods used may not be detailed fully beforehand, increasing the risk of author bias. However, the impact of guideline authors' biases can be reduced by having a defined protocol for guideline development, as with clinical trials. A transparent and robust guideline protocol can also help to achieve recognition from relevant professional organizations. In this study we describe the protocol for the construction of internationally agreed-upon guidelines for the diagnosis and management of IBM. In this work we aim to: (1) identify and navigate the practical challenges of producing evidence-based guidance, informing future clinical guideline construction; and (2) provide a transparent guideline development process that minimizes methodological bias.

METHODS

Guideline Scope. Clinical guidelines will be developed (Table 1) for the diagnosis and management of sporadic IBM, excluding the unrelated group of conditions known as hereditary inclusion-body myopathies (sometimes abbreviated to h-IBM). This guidance is intended to be internationally applicable and will identify potential cost implications where appropriate. However, the guidance will not involve health economic analysis, which may be subject to variations in different health-care systems.

The Guideline Development Group. We will establish a multidisciplinary Guideline Development Group (GDG) composed of physicians, allied health-care professionals, and patient representatives from different countries. Signed declaration of interest forms will be collected from all collaborators. The GDG members will then be assigned to 1 of 5 sectional themes on: (1) diagnosis; (2) drug treatment; (3) physical and practical management; (4) respiration, nutrition, and cardiac management; and (5) living with IBM, which will cover aspects of psychosocial management and multidisciplinary care. Each section steering committee will have a nominated section lead and between 7 and 9 other members, provisionally identified through the ENMC International Workshop.[8] The "Living with IBM" section will specifically include patient representation.

Table 1. Stages of clinical guideline development, adapted from the NICE guidelines manual.[21]

Prepare the scope
Select guideline development group members
Refine and agree upon review questions
Agree upon guideline methodology
Identify the research evidence
Review the research evidence
Develop recommendations using a Delphi-type approach
Prepare the guideline draft
Make plans for implementation
Revise guideline in light of stakeholder comments
Finalize implementation support based on the final guideline
Prepare and publish final guideline and implementation tools
Update the guideline and/or correct errors

Clinical Questions. All 5 sections will discuss and agree on clinical questions for the guidelines to address, which will help to frame the content of the literature review and provide a context for formation of recommendation statements. The agreed-upon questions will use a Patient/Population, Intervention, Comparator, Outcome (PICO) format and will relate to the broad sectional themes, encompassing therapeutic, diagnostic, prognostic, population screening, and causation categories.[15] It is anticipated that some questions may be identified as unanswerable on review and will encourage further research. We also expect new questions to arise during guideline development, which could be explored in future guideline updates.

Literature Search. Our literature search will include randomized and non-randomized studies. We will complete an initial overarching search of CINAHL (January 1981 to present), EMBASE (January 1980 to present), MEDLINE (1946 to present), and PsychINFO (1806 to present), with filters for English language and human studies. Ongoing trials will be identified through ClinicalTrials.gov (https://clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/). Databases will be searched again before guideline publication, allowing the section steering committees to reference any new studies.

Data Extraction and Critical Appraisal. Titles and abstracts of articles identified by the literature search will be screened by at least 2 GDG members (K.J. and section lead), and relevant full-text articles will be obtained for critical appraisal. Only publications that present primary data will be considered

for data extraction. Abstract-only publications, theses, narrative reviews, and any studies not related to sporadic IBM will be excluded from the literature appraisal.

Each section steering committee will complete a literature review within the context of their agreed-upon clinical questions. In the absence of enough evidence for data extraction, section leads (D.H.J., J.S., A.W., U.B., and M.R.) will disseminate each agreed-upon clinical question to at least 2 members for literature review. If sufficient evidence is available for data extraction, the section leads will directly allocate literature for review to section members. Each publication will undergo data extraction by at least 2 section members using an agreed-upon data collection form tailored to the type of study design. These data collection forms will be summarized by a section member, and the summary will be reviewed by both members who complete data extraction. Any discrepancy in critical appraisal will be resolved by another section member or the guideline coordinator (K.J.) following review of the publication, summary, and both data collection forms. This collaborative approach to literature appraisal is expected to aid the process of forming potential recommendation statements for Delphi-based consensus.

Randomized or quasi-RCTs will be assessed by the GRADE process, as an internationally adopted approach for assessing evidence quality.[16] For the critical appraisal of non-randomized studies we will use the Critical Appraisal Skills Programme (CASP).[17] This internationally available learning resource includes 8 critical appraisal tools, which are used to support health-care practitioners with structured and consistent evaluation of systematic reviews, RCTs, cohort studies, case–control studies, economic evaluations, diagnostic studies, qualitative studies, and clinical prediction rules. If at least 2 GDG members agree that none of the CASP checklist study design criteria are met (e.g., in case series or individual case reports), then such studies can instead be appraised using an alternative, custom-designed data extraction form based on the PICO algorithm,[18] which has been used to help formulate answerable research questions.

Agreeing upon Expert Opinion. The GDG lead and coordinator will open a 3-round consultation process (Table 2) by proposing possible statements corresponding to the clinical questions raised by the section steering committees. These statements will be presented to section steering committees in the context of findings from the literature review. To encourage wider expert participation, specialists from other sections of the GDG will be invited to join the consultation, and the section steering committees will also be invited to nominate additional experts from outside of the GDG. The steering committees' prior completion of collaborative critical appraisal is expected to optimize the quality and accountability of expert agreed-upon recommendations.

Table 2. Use of a Delphi-type approach to generate statements of recommendation

Round 1 options
1. Accept statement for recommendation
2. Remove statement
3. Place statement under consideration for recommendation
4. This statement is outside of my expertise
5. Other—add/rephrase statement
   - *Delete statements where > 50% indicate "Remove statement"*
   - *All remaining statements are carried forward to the next round*

Round 2 options

As per Round 1, but following e-mail discussions of Round 1 results within each section steering committee

Round 3 options
1. Accept recommendation statement
2. Remove statement
3. Place statement under consideration for recommendation
4. This statement is outside of my expertise
   - *Delete statements where > 50% indicate "Remove statement"*
   - *Consensus recommendation statements are accepted if at least 70% agree*
   - *Remaining statements are placed under consideration for recommendation and discussed in relation to the number of respondents indicating that statements are outside of their expertise*

Delphi-type consultation will produce recommendation statements that are: (1) consensually agreed upon by an expert panel; and (2) based on individual, anonymous evaluation. The method proposed assesses the necessity of statements, allowing statements to be added or removed. Moreover the strength of each included statement is evaluated implicitly according to the level of expert agreement and uncertainty. This Delphi-type approach and the percentage cut-offs used are partly modeled on consultations conducted previously to select outcome measures and to develop quality assessment tools.[19,20] Guidance on the wording of statements included in the consultation will be provided before each round of consultation. Post-consultation review of the statements will be completed by the guideline producers, and accepted statements will be organized according to their strength, based on the explicit use of the conditional clause (e.g., "should" or "could"), as applied in other published guidelines.[21]

The Delphi process will be conducted online, via SurveyMonkey, Inc.[22] Anonymized results from each round of the Delphi process will be circulated to participants by the GDG coordinator for consideration. A free-text "Comments" box will also be

included at the end of each consultation's list of statements so that participants' commentary (also anonymized) can be circulated for consideration alongside the consultation results. Each section steering committee will engage in e-mail discussions of the results from Round 1 in order to facilitate interactive discussion before Round 2 of the consultation.

The draft guidance will be presented and discussed at a workshop meeting of GDG members, patients, and other stakeholders. This meeting will provide an opportunity for discussion of the guideline findings and facilitate wider stakeholder participation to consolidate dissemination and implementation plans. We anticipate the finalized guidelines will be published in an open-access format to promote dissemination. Guideline implementation will be supported through the development of audit tools by GDG members. Evaluation of the guideline construction will also be incorporated into the process through written feedback from guideline contributors. Finally, accreditation of the guidelines will be sought from national professional organizations to increase regional dissemination and their use in clinical practice.

DISCUSSION

This protocol for developing clinical guidelines has highlighted practical issues in existing guideline processes and outlines a novel approach to formulating recommendations through a nonhierarchical assessment of the literature and canvassing of expert opinion. Systematic review of existing guidelines has shown that most guideline producers do not report their guideline methodology transparently, which reduces their validity and credibility.[23,24] Furthermore, a lack of reporting on guideline evaluation and implementation similarly reduces the quality of the guideline process.[24] These considerations in guideline construction have been integrated into our guideline protocol to enhance its robustness as a novel process and to satisfy accreditation requirements of guideline development organizations, such as NICE. Attaining guideline accreditation by NICE and similar national organizations is crucial for supporting the dissemination and uptake of the guideline as a trusted source of information. Meanwhile, the prioritization of local issues for implementation is expected to require further input from a range of stakeholders both during and after guideline construction.

A systematic approach to developing clinical recommendations is essential for limiting the reporting bias of enthusiastic contributors beyond the existing knowledge base. Similarly, guideline bias in favor of dominant individual experts also needs to be minimized in the construction of international multidisciplinary care guidelines. We have developed a Delphi-type method to facilitate the contribution of a range of experts from different countries in the development of clinical guidelines. Yet, the breadth of expertise and disciplines covered by the guidelines could potentially dilute specialist expert opinion, emphasizing the need for further post-consultation discussion within section steering committees.

In terms of systematic review of the evidence base, there are a variety of methods used for data extraction and critical appraisal. The process of data extraction needs to be standardized but also tailored to the type of study under consideration, which the CASP resources largely facilitate; a PICO appraisal can easily be applied to allow standardized data extraction of those studies that do not clearly conform to any study design covered by CASP, such as case reports. In appraising the evidence we chose to avoid hierarchical ranking (e.g., alphabetical or numerical), which can weaken clinical recommendations for which RCT-level evidence may be inappropriate or unattainable. Through applying mixed methods, we anticipate that guideline statements will address the clinical questions raised using a range of supporting evidence and expertise, and this will be made transparent in summary-of-findings tables.

The financial implications of clinical guidelines can be a major barrier to their implementation, yet they are often ignored by guideline producers.[23] The scope of these clinical guidelines is to consider potential costs where possible. However, as international guidelines, the costing for implementing recommendation statements is expected to vary with the health care systems of each country. We have therefore taken the decision to not incorporate a health economic analysis into the current guideline protocol, although subsequent economic evaluation would be recommended to account for local variations in healthcare systems and resource expenditure. Any deviations from the protocol will be detailed and explained in the published guidelines.

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