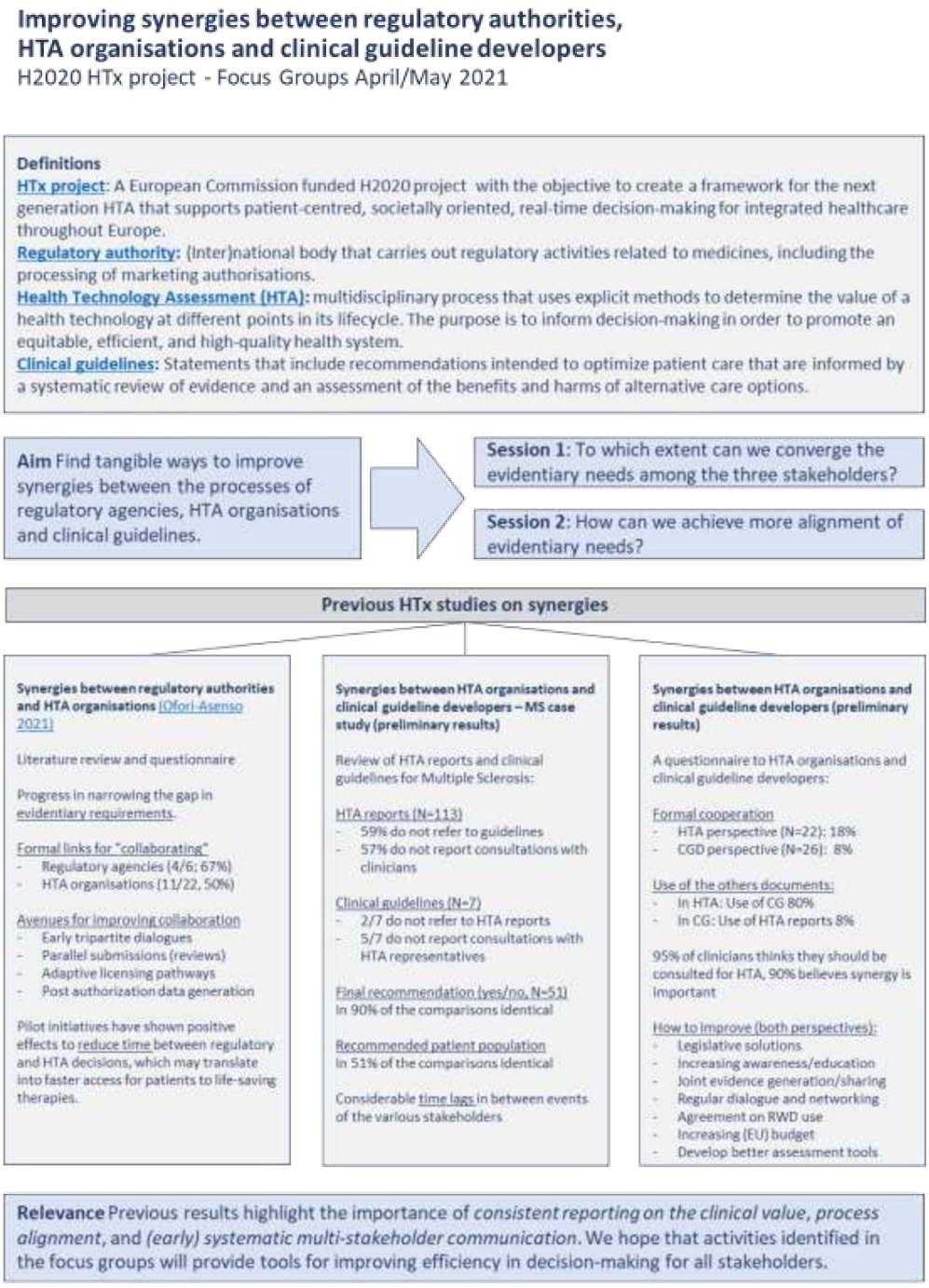
Supplement 1. Information sheets disseminated to participants in preparation of the focus groups



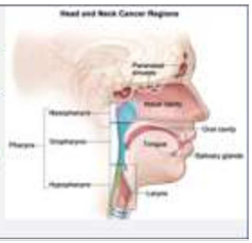
Improving synergies between regulatory authorities, HTA organisations and clinical guideline developers

Case Study: Head and neck cancer

H2020 HTx project - Focus Groups April/May 2021

Head and neck (H&N) cancer

H&N cancer is a collective term for tumours in the upper aerodigestive tract, from lips to voice box. The most prevalent are squamous cell carcinomas (SCCHN) with approximately 12 cases per 100.000 in 2018 (4% of all tumours). A rarer form is nasopharyngeal cancer (NPC) with 0.4-2.1 cases per 100.000 in 2018. Symptoms of head and neck cancer can be expressed by a *lump in the neck, sore tong or throat, bleeding areas, painful or difficult swallowing, and persistent hoarseness and/or a blocked nose*. Risk factors of H&N cancer include tobacco and alcohol use and increasingly the human papillomavirus. The treatment of H&N cancer is multidisciplinary and depends on the tumour's histology, location and stage. See the guidelines by Machiels et al. and Bossi et al. for more information.



Treatment SCCHN

Stage I-II: tumour <4 cm
Stage III-IV: tumour >4 cm + lymph nodes or distant organs

- (Transoral) surgery
- Radiotherapy
  - Intensity-modulated
  - Volumetric-modulated arc therapy
- Systemic therapy (cisplatin, 5-fluorouracil, cetuximab)
  - As induction before radiotherapy
  - Concomitant with radiotherapy

Recurrent or metastatic (as mono- or combination therapy)

- Targeted therapies: pembrolizumab, nivolumab
- methotrexate, taxanes, platinums, 5-fluorouracil, cetuximab

Treatment NPC

Involves radiotherapeutic and surgical strategies as in SCCHN. Systemic treatments include:

- chemotherapy (cisplatin, oxaliplatin, gemcitabine, capecitabine, paclitaxel, docetaxel, 5-fluorouracil, irinotecan, vinorelbine, ifosfamide, doxorubicin)
- targeted therapy (nivolumab, pembrolizumab, cetuximab)

Proton therapy

Leeman et al. published in the Lancet in 2017:
"Use of proton beam therapy has expanded worldwide. Physical characteristics of the proton beam offer important advantages versus widely used photon techniques (i.e. radiotherapy) in terms of radiation precision. In head and neck cancer in particular, proton beam therapy is uniquely suited for the complex anatomy of tumours and sensitive surrounding organs."

Outcome measures (few examples, not limited to)

- Loco-regional recurrence
- Morbidity due to toxicity

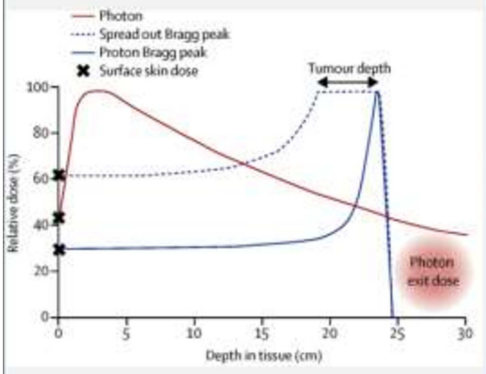
Swallowing:

- Rosenbeck's Penetration-Aspiration Scale (PAS)
- The 100 ml Water Swallow Test (WST)
- The Performance Status Scale: Normalcy of Diet and the MD Anderson Dysphagia Inventory (MDADI)

Patient Reported Outcome Measures:

- 12-item (partial) Vanderbilt Head & Neck Symptom Survey
  - Dysgeusia, pain, mucositis, weight loss due to swallowing, mucus causing choking/gagging, etc.

Proton versus photon therapy depth-dose curves



Clinical trials for H&N cancer

European randomized trials comparing protons to photons therapy for H&N cancer.

Trial	Country	Year of activation	Proton/photon	Population	No. patients
DAHANCA 35	Denmark	2020	2/1	SCC of the pharynx or larynx	500
IMPERATOR	Netherlands	Unknown	1/1	Locally advanced SCCHN	350
TORPEdO	UK	2020	2/1	Oropharyngeal	180

Improving synergies between regulatory authorities, HTA organisations and clinical guideline developers

Case Study: Type 1 and 2 diabetes mellitus

H2020 HTx project - Focus Groups April/May 2021

Type 1 and 2 diabetes mellitus High glucose levels in diabetes mellitus are due beta cells in the pancreas that no longer produce (sufficient) insulin, or to resistance of the body's skeletal muscle cells to insulin. Type 1 is caused by an autoimmune response against pancreatic beta cells and generally has a genetic origin with a juvenile onset. Type 2 patients often develop the disease later in life due insulin resistance caused by age, excess body weight, an unhealthy diet or a lack of exercise. Lastly, DM can be induced during pregnancy. The risk of DM is with the complications caused by high glucose levels, such as *cardiovascular disease, nephropathy, neuropathy, retinopathy*. In recent years, devices and e-health have emerged to support the management of glucose levels and insulin intake.

Insulin (generally for T1DM or uncontrolled T2DM)

Group	Insulin	Brand	Effect	Duration
Rapid-acting	aspart, glulisine, lispro	Novorapid, Fiasp, Apidra, Humalog	15 min	2-4 hours
Regular/short-acting	regular	Actrapid, Humuline, Insuman	30 min	3-6 hours
Intermediate-acting	NPH	Humuline, Insulatard, Insuman	2-4 hours	12-18 hours
Long-acting	detemir, glargine	Levemir, Lantus, Toujeo, Abasaglar	Several hours	24 hours
Ultra long-acting	degludec	Tresiba	Several hours	42 hours

Systemic treatments (generally for T2DM, sometimes T1DM)

Classification	Drug group	Drug
Traditional	Biguanides	metformin
	Sulfonylureas	glimepiride glibenclamide gliclazide tolbutamide
	thiazolidinediones	rosiglitazone (Avandia, *withdrawn*) Pioglitazone (Actos)
New generation	DPP-4 inhibitors	linagliptin (Trajenta) saxagliptin (Onglyza) sitagliptin (Januvia) vildagliptin (Galvus)
	SGLT2 inhibitors	canagliflozin (Invokana) dapagliflozin (Forxiga) empagliflozin (Jardiance) ertugliflozine (Steglatro)
	GLP1 agonists	Lixisenatide (Lyxumia) Dulaglutide (Trulicity) Exenatide (Byetta, Bydureon) Liraglutide (Victoza, Sadenda) Semaglutide (Ozempic, Rybelsus)
Other	Other	Nateglinide, repaglinide, acarbose, miglitol, colesevelam, bromocriptine

Devices (overview American Diabetes Association, 2019)

Insulin delivery

- Insulin syringes and pens (used by most patients, "Smart" pens can calculate insulin doses and provide data reports)
- Insulin pumps (continuous subcutaneous insulin injection)

Self-monitoring blood glucose

SMBG is an integral component of effective therapy of patients taking insulin, often included in clinical trials. Recently, CGM has emerged as a complementary method for the assessment of glucose levels.

Continuous glucose monitors

- Most CGM devices are real-time, which continuously report glucose levels and include alarms for hypoglycemic and hyperglycemic excursions.
- The other type of device is intermittently scanning CGM (isCGM).

Automated insulin deliveries

An insulin pump, a continuous glucose sensor, and an algorithm that determines insulin delivery.

Diabetes e-health technologies (overview Fleming et al. 2020)

Category name	Description/definition
Nutrition apps	Monitor carbohydrate, fat, protein and energy content Meal planning and insulin dose adjustment
Physical activity apps	Track activity, count calories and set goals for exercise and weight management
Glucose monitoring apps	Glucose measurement and control
Insulin titration apps	Calculation of basal, prandial and correction insulin doses
Insulin delivery apps	Collect and display data on insulin pumps and smart pens Offer decision support

Outcome measures (not limited to)

Outcome Measures*
Reducing risk of heart attacks
Reducing hemoglobin A1c levels
Avoiding hypoglycemic events/episodes of low blood sugar
Reducing risk of stroke
Reducing risk of diabetes-related amputations and foot ulcers
Reducing risk of diabetes-related kidney disease
Reducing risk of diabetes-related neuropathy/nerve damage
Reducing risk of emergency room visits from diabetes
Reducing risk of diabetes-related retinopathy/eye disease*
Reducing risk of hospitalizations from diabetes
Improving quality of life
Weight loss

Treatment guidelines The treatment of DM may include a combination of all the abovementioned interventions, including lifestyle interventions. Finding the right treatment combination is a quest. It should fit withing the patient's lifestyle and be effective at maintaining low blood glucose levels (over time expressed in the HbA1c) as to prevent development of complications and mortality of these complications. There are numerous guidelines available. These are examples on precision medicine in DM, cardiovascular complications, insulin therapy, hyperglycemia in type 2.

Improving synergies between regulatory authorities, HTA organisations and clinical guideline developers

Case Study: Multiple Sclerosis

H2020 HTx project - Focus Groups April/May 2021

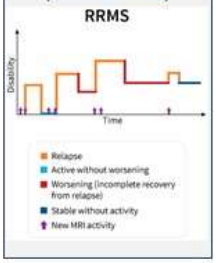
Multiple Sclerosis (MS)

Yearly, MS affects roughly 2,1 out of 100.000 people worldwide. The disease involves an immune-mediated reaction against the body's central nervous system (CNS), including the brain, spinal cord and optic nerves. This process hinders or completely stops the signals within the CNS creating a variety of neurological symptoms that varies in type and severity. Symptoms include *fatigue, walking difficulties, numbness or tingling, spasticity, weakness of muscles, problems with vision, dizziness, bladder problems, sexual problems, bowel problems, pain and/or itching, cognitive and emotional changes, depression* and several other, less common symptoms. The cause of MS is not fully understood, but it is believed to involve genetic susceptibility, abnormalities in the immune system and environmental factors. MS can be expressed in different types of disease, as shown below (Lublin et al. 2014). Note that there is some discussion on the various phenotypes of MS, see here more information.

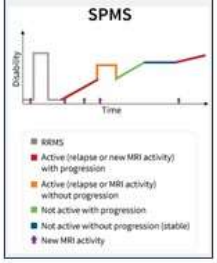
Clinically Isolated Syndrome (CIS)

CIS is a first episode of neurologic symptoms, which lasts for at least 24 hours. It is characteristic of MS but does not yet meet the criteria for a diagnosis of MS. People who experience a CIS may or may not go on to develop MS.

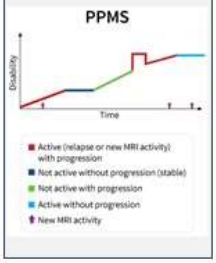
Relapsing-Remitting (80% of MS cases)



Secondary Progressive



Primary Progressive



(Disease-modifying) treatments for MS

Trade name	Active Substance	Authorized	EMA indication (with link)
Betaferon	interferon beta-1b	1995	CIS, RRMS, SPMS
Avonex	interferon beta-1a	1997	CIS, Relapsing MS
Rebif	interferon beta-1a	1998	CIS, Relapsing MS
Novantrone / Eslep	mitoxantrone	1998	Highly active relapsing MS
Copaxone	glatiramer acetate	2004	*Not assessed by EMA*
Tysabri	natalizumab	2006	Highly active RRMS
Extavia	interferon beta-1b	2008	CIS, RRMS, SPMS
Gilenya	fingolimod	2011	Highly active RRMS
Fampyra	fampridine	2017	MS (EDSS 4-7)
Lemtrada	alemtuzumab	2013	RRMS
Aubagio	teriflunomide	2013	RRMS
Tecfidera	dimethylfumarate	2014	RRMS
Plegridy	peginterferon beta 1-a	2014	RRMS
Mavenclad	cladribine	2017	Highly active RRMS
Ocrevus	ocrelizumab	2018	Relapsing MS, PPMS
Zinbryta	daclizumab	2018	*Withdrawn*
Mayzent	siponimod	2020	SPMS
Zeposia	ozanimod	2020	RRMS
Kesimpta	ofatumumab	2021?	*Pending*
Rituxan + generics	rituximab	Not for MS	*Off-lable*

The Expanded Disability Status Scale (EDSS)

0 Examination shows everything is normal
1 No disability, very small sign that one function isn't normal
2 Very small disability in one function
3 Moderate disability in one function or mild disability in three or four functions. No problem walking
4 Significant disability but you can walk without an aid for 500 metres
5 Disability gets in the way of daily activities, but you can walk without an aid for 200 metres
6 You can walk 100 metres with a stick or crutch, with or without rests
7 Essentially restricted to a wheelchair but active all day; you can't walk more than 5 metres even with an aid
8 Basically, you need to be in a chair, wheelchair or bed. You may be out of bed much of the day. You can use your arms
9 In bed all the time but you can communicate and eat/swallow
10 Death due to MS

For other MS outcome measures, such as the timed 25 foot walk, the 9-Hole Peg Test and the MS Quality of Life, see this link.

Treatment algorithm

Treatment algorithms vary widely across countries, even across hospitals. For more information, you can access the ECTRIMS/EAN guideline via this link.

 This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement № 825162.

Improving synergies between regulatory authorities, HTA organisations and clinical guideline developers

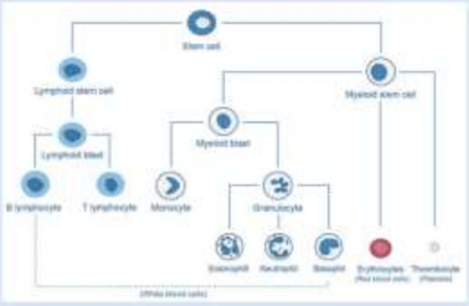
Case Study: Myelodysplastic syndromes

H2020 HTx project - Focus Groups April/May 2021

Myelodysplastic syndromes (MDS)

MDS is a collective term for bone marrow malignancies in which blood cells in the bone marrow do not fully mature. It is a rare disease (4 in 100.000 in the U.S. annually) that may have its onset at any age, though it predominantly affects the population over 70. Six types of MDS (below) are categorized by the World Health Organisation (WHO) differing in severity, from indolent for years to very fast developing aggressive forms. Patients with MDS may develop *anaemia, neutropenia, thrombocytopenia* that is expressed in *chronic fatigue, weakness or tiredness, breathless, bruising or easy bleeding and an increased risk at infections.* Transformation into acute myeloid leukaemia (AML) occurs in around 30% of MDS patients.

From the MDS UK Patient handbook:



MDS with single lineage dysplasia (MDS-SLD)

Only one type of blood cell has become abnormal

MDS with multilineage dysplasia (MDS-MLD)

Two or more types of blood cell have become abnormal

MDS with ring sideroblasts (MDS-RS)

One or more types of cells with iron ring (sideroblasts)

MDS with excess blasts (MDS-EB)

Number of blast cells in the blood and bone marrow higher than normal

MDS with isolated del(5q) or 1 additional abnormality

cells in bone marrow have a isolated del (5q)

MDS, unclassifiable (MDS-U)

Any type of MDS which does not fit into any of the other categories

IPSS-r

The International Prognostic Scoring System (IPSS-r) for MDS describes the expected risk of developing AML and survival, based on diagnostic tests:

- full blood counts
- number of abnormal immature cells (blasts) from bone marrow sample
- a chromosome test from the bone marrow

Risk category	Risk score	Median survival in years	Median time (years) to 25% AML evolution
Very low	≤1.5	8.8	Not reached
Low	>1.5–3.0	5.3	10.8
Intermediate	>3.0–4.5	3.0	3.2
High	>4.5–6.0	1.6	1.4
Very high	>6.0	0.5	0.73

Patiënt reported outcome measures (Stauder et al. 2020)

- Cancer-specific: EORTC QLQ-C30, FACT-An
- Generic: SF-36, EQ-5D
- MDS- and AML-specific instruments: QUALMS and QOL-E in MDS; FACT-Leu and EORTC QLQ-Leu in AML

Other outcome measures:

Independence from or reduction in need for transfusion, increase in Hb, reduction in abnormal cells, cytogenetic remission

Treatment options as described by MDS Europe

Symptomatic treatments include blood transfusion, chelation therapy (deferoxamine, deferasirox, deferiprone) and measures to avoid infection. Disease-modifying therapies are described below. Treatment decision is dependent of many factors including age, risk score, MDS type and fitness of the patient. Various treatment guidelines can be accessed through this link.

Type of treatment	Drug	Indication
Growth factors	Erythropoietin alpha or beta, darbopotein Granulocyte colony-stimulating factor (G-CSF)	(very) low or intermediate IPSS score
Immunosuppressants	Anti-thymocyte globulins (ATGs) and ciclosporin A	(very) low or intermediate IPSS score
Targeted therapy	Lenalidomide (Revlimid)	(very) low or intermediate IPSS score associated with isolated del (5q)
	Luspatercept (Reblozyl)	MDS with ring sideroblasts
	Azacitidine (Vidaza)	Intermediate or (very) high risk MDS
Donor stem cell transplant (allogeneic)	Treosulfan (Trecondi)	Fit patients, generally with higher IPSS scores, or lower risk after failure of initial treatment or with complicating features
Chemotherapy	e.g. daunorubicine and cytarabine	(very) high IPSS score
Other	Imatinib (Glivec)	re-arrangements of the gene for platelet-derived growth factor receptor (PDGFR)

Supplement 2. Focus Group Participants

Table S2. Overview of the focus group participants.

Perspective	Consent to be listed with name/ institution	Full name	Organisation	Country
Clinician	Yes	David Bowen	Leeds University Hospital	England
Clinician	Yes	Jako Burgers	Nederlands Huisartsen Genootschap	Netherlands
Clinician	Yes	Giancarlo Comi	European Charcot Foundation	Italy
Clinician	Yes	Rosa Corcoy	Hospital de Sant Pau	Spain
Clinician	Yes	Vincent Gregoire	Centre Leon Berard	France
Clinician	Yes	Hans-Peter Hartung	University Düsseldorf	Germany
Clinician	Yes	Eva Havrdova	Charles University	Czech Republic
Clinician	Yes	Brigit de Jong	Academic Medical Centre Amsterdam	Netherlands
Clinician	Yes	Hans Langedijk	University Medical Centre Groningen	Netherlands
Clinician	Yes	Maddalena Lettino	San Gerardo Hospital	Italy
Clinician	Yes	Luca Malcovati	University of Pavia	Italy
Clinician	Yes	Bianca Rocca	Policlinico Universitario A. Gemelli	Italy
Clinician	Yes	Theo de Witte	Radboud University Medical Centre	Netherlands
Clinician	Yes	Piotr Zsymanski	Center for Postgraduate Education, and Clinical Cardiology Center, Central Clinical Hospital MSWiA	Poland
HTA	Yes	Amanda Adler	National Institute for Health and Care Excellence	England
HTA	No (indicated that due to limited contribution)	Anonymous	Anonymous	France
HTA	Yes	Nick Crabb	National Institute for Health and Care Excellence	England
HTA	Yes	Noreen Downes	Scottish Medicines Consortium	Scotland
HTA	Yes	Karen Facey	Evidence based health policy consultant	England
HTA	No response to request	Anonymous	Anonymours	Romania
HTA	Yes	Cláudia Furtado	Infarmed	Portugal
HTA	Yes	Niklas Hedberg	Dental and Pharmaceutical Benefits Agency	Sweden
HTA	Yes	Andrej Janzic	Ministry of Health Slovenia	Slovenia
HTA	No response to request	Anonymous	Anonymous	Poland
HTA	Yes	Emilia Mavrokordatou	Ministry of Health Cyprus	Cyprus
HTA	Yes	Gergo Meresz	The National Institute of Pharmacy and Nutrition	Hungary
HTA	Yes	Anna Nachtnebel	Federation of Social Insurances	Austria
HTA	Yes	Bhash Naidoo	National Institute for Health and Care Excellence	England
HTA	Yes	Krista Schutte	Dutch National Health Care Institute	Netherlands
HTA	Yes	Tomas Tesar	Comenius University, Faculty of Pharmacy	Slovakia
HTA	Yes	Fredrik Tholander	Socialstyrelsen	Sweden
HTA	Yes	Lesley Tilson	National Centre for Pharmacoeconomics	Ireland
HTA	Yes	Ly Tran	Dutch National Health Care Institute	Netherlands
HTA	Yes	Wojciech Wysoczanski	Agency for Health Technology Assessment and Tariff System	Poland
HTA/ Regulator	Yes	Krystyna Hviding	Norwegian Medicines Agency	Norway
Regulator	Yes	Michael Berntgen	European Medicines Agency	Netherlands

Regulator	Yes	Pero Draganic	Agency for medicinal products and medical devices	Croatia
Regulator	Yes	Hans-Georg Eichler	European Medicines Agency	Austria
Regulator	Yes	Peter Mol	Medicines Evaluation Board	Netherlands
Regulator	Yes	Daniel O'Connor	Medicines and Healthcare products Regulatory Agency	United Kingdom
Regulator	No response to request	Anonymous	Anonymous	Sweden
Regulator/ HTA	Yes	Anja Schiel	Norwegian Medicines Agency	Norway

Supplement 3. Guide for moderators | HTx Focus Group Synergies
April 26th and May 10th

Next Generation Health Technology Assessment

Aim

Our research aims to *find tangible ways to increase synergy* between the processes, and therewith outcomes, of regulatory agencies, HTA organisations and clinical guidelines. After previous work on existing synergies between regulatory authorisations, HTA organisations and clinical guideline developers, this study is set to identify activities to increase the synergy between those stakeholders. We will explore the views of all three of the stakeholders to explicate existing hurdles and necessary facilitators for increasing synergy.

Research questions:

1. *To which extent can we converge evidentiary needs among stakeholders?*
2. *How can we achieve convergence of evidentiary needs among stakeholders?*

General remarks

- ***First thing when entering the break-out room is ensuring that it is recorded!!!***
- The focus groups will last for 60 minutes per topic.
- Start each of the two focus groups with the defined research question and let all the participants, one by one, respond to it. This way, everyone is heard and more comfortable with engaging in further discussions.
- If there is a minimal response, make the questions more specific by asking one of the follow-up questions.
- The bold subquestions are the most important ones.
- Let participants guide the conversation and speak into detail, only steer them if the discussion becomes too much off topic.
- Ask a lot of open follow-up questions to reach a deep level of detail and underlying arguments, specifically if participants disagree.
- It is okay if not all the subquestions are discussed, just make sure that relevant questions are discussed.
- Use the whatsapp group (HTx Focus Groups Synergies) in case anything does not go as planned.
- The second moderator should keep track of the time.
- You can use the powerpoint slides as a back up if needed in the discussion, these include:
    - the research questions and subquestions,
    - a summary of results of previous research in HTx,
    - a summary of relevent aspects from the case study.

Topic 1

To which extent can we converge evidentiary needs among stakeholders?

What are the crucial and feasible assessment criteria to align among regulatory authorities, HTA organisations, and clinical guideline developers (according to the PICOT framework)?

- How to define relevant patient populations and subgroup analysis?
  - Definition of unmet medical need
- How to agree on characteristics of the intervention?
  - Dosing
  - Positioning
  - Combinations
  - Sequences
  - Concomitant diagnostics
  - Monitoring biomarkers
- How to determine the rightful comparator?
  - Placebo
  - Standard of care
- How to decide on acceptable outcomes?
  - Primary endpoint
  - Secondary endpoint
  - Hard or surrogate endpoints
  - Patient reported oucome measures (PROMS)
  - Quality of life
  - Patient preferences
- How to determine the appropriate trial design?
  - RCT or other
  - Active comparator arm

Topic 2

How can we achieve convergence of evidentiary needs among stakeholders?

How can we employ methods to achieve convergence among stakeholders?

- Which methods are or can be used in the stakeholders tasks?
  - For example, assessing trial quality with GRADE
- If you would work through similar methods, what would you win and what would you lose?

How can we use early stakeholder dialogue to achieve convergence?

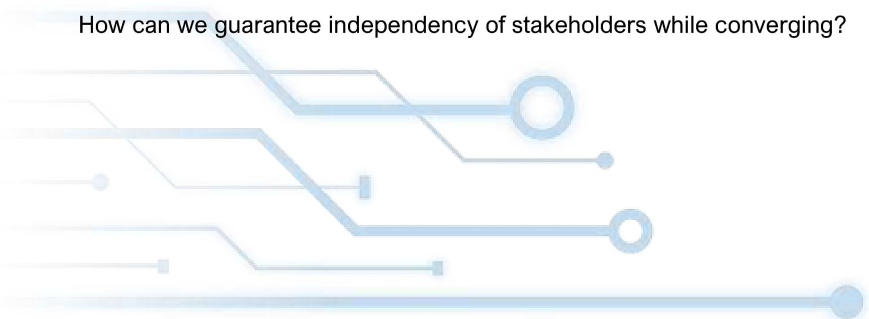
- When in the process should these conversation(s) take place?
- Who should be involved in these conversations?
- Which topics are most relevant to discuss here? (relates to topic 1)
- Who should initiate or lead these conversations?
- What would potentially prevent you from engaging in stakeholder dialogues?

Are there other potential ways to converge evidentiary needs among stakeholders?

To which extent can we cooperate to achieve convergence?

- Should convergence be about information sharing or actual work load sharing?
- If you would share information or cooperate, what would you win and what would you lose?

How can we guarantee independency of stakeholders while converging?



Supplement 4. Final coding tree and unused codes

Final coding tree as used for results in manuscripts, with number of quotes coded at each.

How may we achieve convergence of evidentiary needs among stakeholders?

- Communication / Stakeholder Interaction (29)
  - Mutual awareness creation (20)
  - Expectations (15)
  - Early Dialogue (60)
  - Joint Scientific Advice (37)
  - Common language or Guidance (17)
    - Aligning definitions (3)
    - Aligning patient population definitions (18)
    - Outcome sets (1)
    - Aligning methods (30)
    - Aligning IT systems (3)
- Implementation (5)
- Transparency (9)
- Culture (2)
- Responsibility or Leadership (24)
- Third party institution or network (7)
- Incentives (22)
- Legislative or political (14)
- Pricing and reimbursement (28)

To which extent can we converge evidentiary needs among stakeholders?

- Independency or Remits (64)
  - Countries (2)
  - Stakeholders (7)
- Data generation (15)
  - Alternative clinical trials (20)
  - Registries and RWD (74)
  - Sharing data (9)
- Priority setting (35)
  - Resources (26)
  - Horizon Scan (8)
  - Unmet Medical Need (11)
  - Devices (4)
- Setting or scope (70)
  - Collaboration or Joint Assessment (9)
  - Timelines (48)
  - Life cycle approach (17)
  - Simplistic approach (15)
- Transferability (40)

Table S4. Codes that have not been used in the final manuscript.

Name	**number of quotes (not mutually exclusive, quotes may be coded as various codes)**
0. Stakeholder interaction	0
Agree	85
Disagree	20
Neutral	184
Bridges	0
HTA-Guideline	51
Reg-Guideline	21
Reg-HTA	38
Examples	4
BeNeLuxA	1
CDF	3
EMA-EUNetHTA advice	7
European Reference Network	4
FDA	7
GIN	1
H2020	1
ILAP	8

Norway HTA-Guideline	2
Pediatrics IMI	2
PRIME	2
Swedish Registry	2
Tasks each stakeholder	0
Academia	9
Clinician	25
Developer	30
EU or EC	6
HTA	14
Insurer	1
Patient	12
Regulator	17
Situation Sketch	0
Clinical relevance	1
Comparator	18
Difference countries	6
Cultural or population	6
Economic	7
Health care (units)	15
Legislative	1
Size	5
Disease specific	0
DM	3
H&N	4
MDS	4
MS	2
Evidence	61
Initial vs post approval data	6
QoL	7
RWD	20
Financial or resource issues	6
HTA deliberation (appraisal)	6
Intervention	5
ATMPs	3
Large number of treatments	10
Later treatment lines	1
Non-pharmaceuticals	9
Off-lable	6
Orphan	1
Speed of development	4
Tumor Agnosts	4
Methods	6
Outcomes	31
OS	3
Uncertainty OS	1
PROMs	7
QoL	24
QoL ADE effect over OS	2
Uncertainty	3
Population	2
Change over time	1
Defining (sub)population	24
Heterogeneity	22
Small population	19
Understanding of disease or diagnosis	14
Unmet Medical Need	7
Process guidelines	36
Process HTA	34
Process regulators	13
Reimbursement or financing	15
Special pathways	2
Trade-off patient vs society	5
Transparency or confidentiality	2

Supplement 5. Participant quotes

Table S5. Ethnographic analysis of participant quotes clustered per theme.

Domain	Quote (stakeholder)
How may we achieve convergence of evidentiary needs among stakeholders?	
Communication	"We now have more communication between [HTA] assessors and neurologists. I think it is very helpful because you can anticipate the position others take and have a much better discussion. It is also better to find solutions for the problems. So, I think that communication between both parties is very crucial." (CLIN)
	"I would say there has been at least some learning, mostly on the individual level. Unfortunately not on the system level. So, it is not that it [parallel scientific advice, red] may suddenly start embracing the needs of the HTA. But for those that have been very often involved in the parallel advices, it has changed their attitude at least, and their understanding." (REG)
	"I value the exchange between payers and regulators for example. This demonstrates my understanding that even though everyone keeps saying "we have different remits", there is still quite a huge information deficit on what this remit actually means. If we exchange on that: What does HTA need? What do they expect? What kind of data? What other methods does EMA apply to establish the benefit/risk? How do they rate the quality of the evidence?" (HTA)
	"That means that the definition of registry itself is not, in my view, sufficiently robust at the European level. Many data are sold as registry data, while they are in fact a retrospective collection of data that are inevitably introducing biases." (CLIN)
	"A practical example: guidelines recommending a special treatment, which has not been approved for that indication. My experience is antithrombotic drugs. Low quality clinical trials, recommending for instance drugs used as monotherapy when there is no approval for these drugs; or the specific example where there has been an approval, but the HTA of that specific country does not approve that drug as a monotherapy." (CLIN)
	"The latest 2019 ESC guidelines are a very good example because you know regarding to the SGLT 2 Inhibitors and the GLP-1 receptor antagonists. There was not huge diversion, but there were some substantial different interpretations of the evidence, as compared to for instance the ADA guidelines, on the same drugs. So, the question was: metformin, with or without? How do you go first line with these patients? Really, the clinical trials were all as add-on strategy, and the guidelines were made as a single strategy." (CLIN)
	"[…] try to identify a common set of outcome criteria for a given disease. For example, can we all agree in diabetes that these are the three or four outcomes that everybody should measure? Irrespective of whether it is in a clinical trial, in an interventional setting, or if it is perhaps even in a routine care, because we know that the routine care data will feed into the knowledge generation." (REG)
Formalized interaction	"I think it [early dialogue] has to start early so that people from different organisations or the different groups feel that the dialogue is meaningful and that there is an opportunity for having an impact in terms of saying, "this is what we need and that can be taken into consideration." (REG)
	"The first empiric trial, which showed the reductions or some benefiting in terms of cardiovascular outcomes, which was the first trial. Then of course, other trials came along but unfortunately, the patient populations were not comparable between the two trials. I think these trials were part of EMA's post-marketing requirements in terms of safety. I wonder why it is not possible at this stage to somehow align that at least on the down-stream units, such as the clinicians or the HTA have then at least this evidence at hand, which is comparable, which allows us to identify those drugs where we willingly pay more." (HTA)
Internal factors	"As I mentioned earlier, I think you have to have a culture that is receptive to working a bit differently." (REG)
	"Guidelines are produced by many different networks and groups of individuals. When dealing with the regulatory entities there should be a process of identifying the relevant

	networks at each specific area. In my view, his should be both top to bottom and vice versa. I think that top to bottom is at a certain point required. The introduction, for instance in the field of rare disease, of European Reference Networks is an example. But these top to bottom processes must be sensitive to the existing bottom to top initiatives as these initiatives have to be reconnected to the existing networks that in some cases, if not most cases, are representing the scientific and clinical community already existing. So, reconnect is these 2 different processes is critical to have then to establishing a proper framework to develop guidelines and to have an open dialogue between regulatory entities and the community." (CLIN)
	"All drugs for the same indication should fulfil the same rules: how to collect data and how it should be represented, for example. So, we should change our meaning that it is not possible simply first of all, we should start with transparency because when we show the direction when we want to set our goal." (HTA)
	"So, in the end for a general practitioner or for a diabetologist, it can be difficult to reconcile approved indication, HTA assessment and what it is written in the guidelines. They run like 3 routes in parallel and when they cross it is already at the end of the of the story." (CLIN)
External factors	"It would also help the pharmaceutical companies, because if there was some way to try to combine the evidence provided a single evidence package if that were that would be helpful for all of us." (HTA)
	"How many drugs has CHMP retracted because they did not follow up on any conditions of the conditional marketing authorisation or because the special obligations did not turn out? That was exactly one precedent, and it was not the CHMP. It was the European Commission that refused the renewal for that particular drug." (REG)
To which extent can we converge evidentiary needs among stakeholders?	
Data generation	"I like to think about it as the mosaic of evidence generation. We each have our needs as regulators, individual clinicians, as guideline developers and HTA. […] What we are trying to do in most cases, is come together to agree on what I call a core data set. That would be the outcomes etc. […] There will be things where we have parallels with the regulators, or where we have parallels with the guideline developers." (HTA)
	"When we are talking about registries, we have to remember about the pragmatic randomised trials within the registry. So, once we have this system, we are absolutely able to flexibly react to current practice. And it is not necessarily that we have a 10 years' timeline to issue an opinion on a certain technology." (CLIN)
	"It is really the chicken and egg story. We should be collecting RWD, but we do not really have very strong examples of where RWD has really made a massive impact. It is until you have that real impact analysis to say, 'look, we had some key examples where this approach has (semi)revolutionised what we did'." (REG)
	"I think we should share more the information. Again, from EUnetHTA, I had a very good experience getting the EPAR before the publication in order to be able to work with the HTA reports at the early stage." (HTA)
Independency and remits	"Particularly within the MS community, we fear that a too close alliance between the regulatory agency and particularly the reimbursement system and the insurance company might limit the possibilities to find the optimal treatment for patients. So, it is absolutely clear that the evidence should be the same, the goals (besides improving patient's health) may be different." (CLIN)
	"[for collaboration] you can choose either by geography because neighbours usually have some joint systems that they have developed in a similar fashion. Or you can simply look at methodology." (REG)
	"And let us be honest, it would also help the pharmaceutical companies. Because, if there was some way to try to combine the evidence provided a single evidence package that would be helpful for all of us." (HTA)
	"The guidelines arrive at the end of this process, this [early sharing assessments/discussions in a consistent way] could be extremely useful because

	sometimes we spend a lot a lot of time discussing about the strength of evidence and we do not consider the HTA evaluation that could solve some problems" (CLIN)
Scoping the alignment	"Regulators usually say it is a positive or negative decision. You barely take that away, but you could be more explicit in saying the benefit-risks in itself is not enough. The benefit has to be much larger than the little bit that made us give you an approval. […] It is this 'more' where the CHMP is not committing. […] While the HTA organisations are the ones that would say 'no', hard commitment: overall survival of that magnitude has to be proven. Then we would give you a conditional reimbursement." (REG)
	"If we could agree that we do not need the perfect, but that the reasonably good would be good enough, and we pare all this down to four, five questions, not more. Would that enhance our knowledge, or would that diminish our knowledge? Sometimes the perfect is the enemy of the reasonably good. Maybe, have we let the show being run by experts who want it to be it to be very good. And regulators say, 'this is not good enough, this has not been validated and that is not sufficiently sensitive'. All of this with the result that now we have an impractical monster." (REG)
Prioritizing alignment efforts	"I think when products are in really early stage, that it is the time where you can add the most value by having that sort of detailed dialogue. But, I also recognise that if you talk too much about many really early products, there will be high attrition." (HTA)
	"Horizon scanning is important for healthcare systems to be prepared. IHSI is very concretely/operationally. What is coming into the next phase of really knocking on the door? When this is going to be? What is the population going to look like? Which is going to be approved?" (REG)
	"You mentioned about unmet medical need. The definition of unmet medical need is always tricky, but I think a meaningful dialogue and a platform for meaningful dialogue is really resource intensive." (REG)
Transferability	"Generally, because they [pharmaceutical companies] want to be sure that their dossiers are accepted, they propose studies [to HTA organisations in small countries] from the last assessment done at European level. Generally, this is a delay of a couple of years. Even if meanwhile there appears a more recent meta-analysis or other kind of randomized trial that could be synthesized. Something like this, if Europe approved it, it is better to go on the same line. This can create a sort of misbalance about the needs in the national programs, mostly for expensive therapy." (HTA)