Framework to support not-for-profit organisations and academia (institutions and individuals) in drug repurposing by STAMP

July 9th, 2021

Repurposing is the process of identifying a new use for an existing medicine/active substance outside the scope of the original indication

Two different perspectives

Repurposing leaded by MAH

- Normally, a MAH initiates variations, line extensions or submit a new medicinal product with the repurposed indication
- However, the industry very often lack commercial incentives or, when exists, it seems very often disproportionate

Repurposing leaded by other agents

- A not-for-profit party is more oriented to products that are <u>off-patent and out of regulatory protection</u>
- However, although involved in generating data, not-for-profit organisations lack of knowledge about regulatory routes and requirements

Consequences of relying in off-label use

- Access to potentially useful new indications may be hampered due to specific regulations or rules
- Old medicines whose main use have turned off-label may disappear
- Repurposing of old, well established medicines into new, over prized medicines introduces invariably tension in health systems (playing against access)

STAMP's framework (I)

- A multistakeholder subgroup of STAMP discussed a framework to provide a visible support to a not-for-profit stakeholder, termed Champion
- The framework* is the process of facilitating data generation and/or data gathering in accordance with regulatory standards of a new therapeutic use for an authorised active substance/medicine
- Only intended for medicines already out of intellectual property/regulatory protection

* https://ec.europa.eu/health/sites/health/files/files/committee/pharm773_repurposing_annex_en.pdf

STAMP's framework (II)

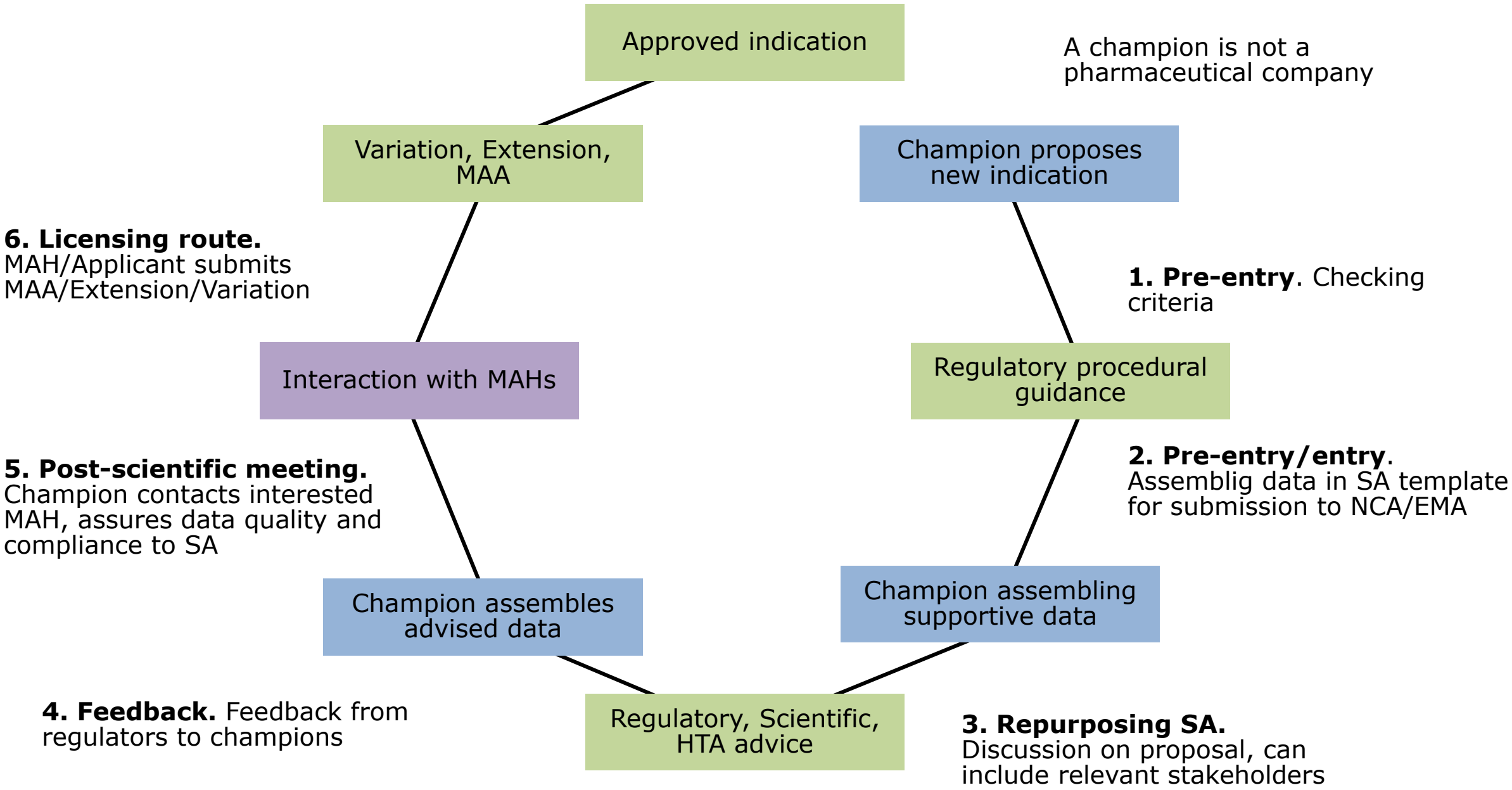
- The Champion is typically a not-for-profit organisation, for example, an entity or a person from a charity or patient group/academic unit/learned society/research funder or payer
- The interaction with the MAH is foreseen in the framework resulting in simple regulatory procedures to include on-label what was previously off-label.
- The framework builds on existing regulatory tools, namely innovation offices and scientific and/or regulatory advice (through EMA and NCA) to provide guidance to champions.

Champion’s roles

- The Champion is able to coordinate and/or foster the research programme up until the point of full industry engagement
- Responsible for liaising and leading the interactions with regulatory authorities and industry/other stakeholders
- Transparent regarding interactions with relevant pharmaceutical company(s)
- In charge of filing the initial request for scientific/regulatory advice on the basis of the available data

Criteria for eligibility (all the following)

- A well-established active substance contained in a medicine with a valid marketing authorisation granted in a Member State or in the European Union.
- Out of data exclusivity and market protection periods and out of basic patent/supplementary protection certificate (SPC) protection.
- Must target a new indication in a condition distinct from the currently authorised indication(s)
- Must target an indication in an area where important public health benefits/Union interests are likely to be achieved

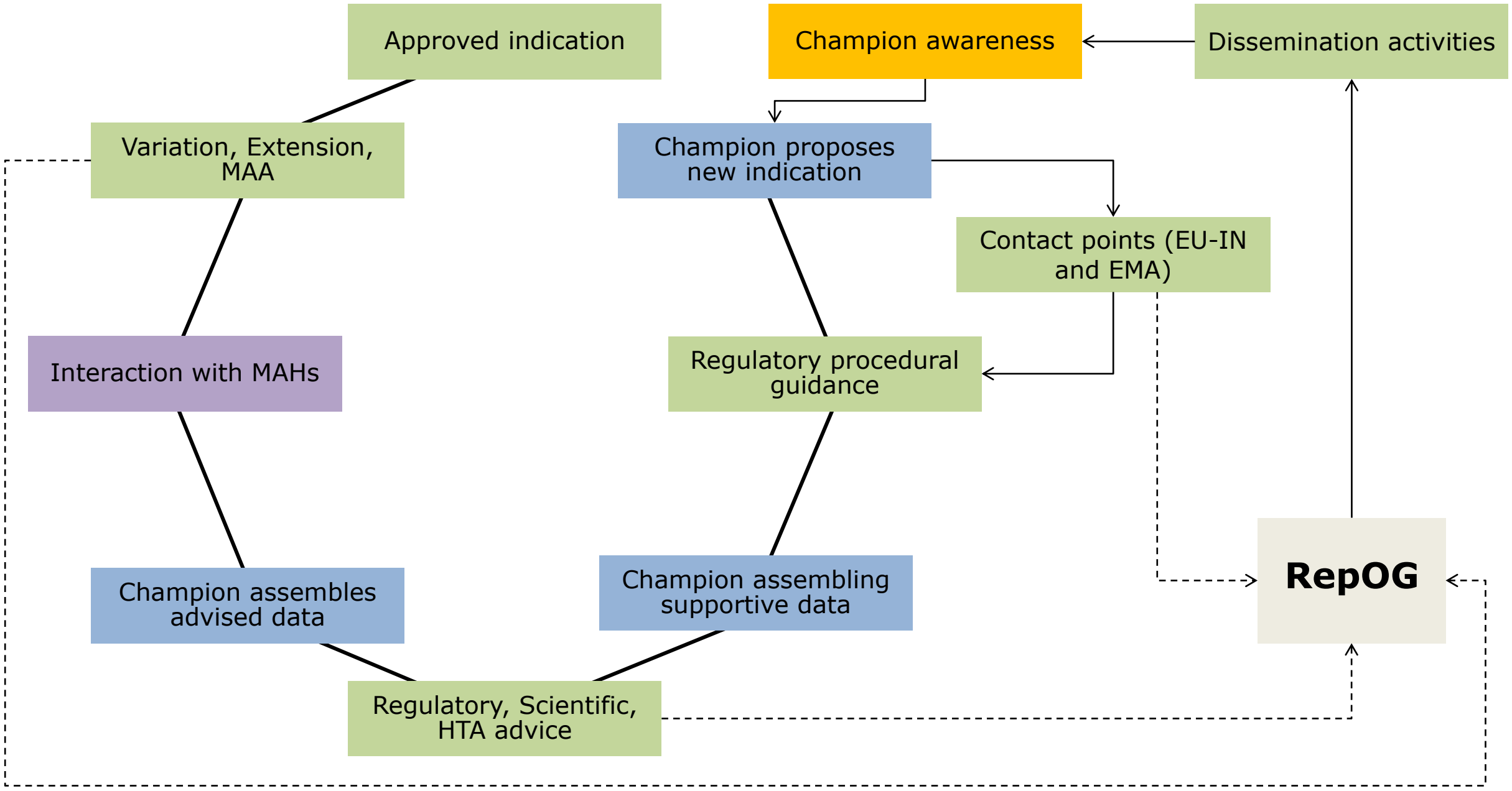

Approved indication
A champion is not a pharmaceutical company
Variation, Extension, MAA
Champion proposes new indication
6. Licensing route. MAH/Applicant submits MAA/Extension/Variation
1. Pre-entry. Checking criteria
Interaction with MAHs
Regulatory procedural guidance
5. Post-scientific meeting. Champion contacts interested MAH, assures data quality and compliance to SA
2. Pre-entry/entry. Assemblig data in SA template for submission to NCA/EMA
Champion assembles advised data
Champion assembling supportive data
4. Feedback. Feedback from regulators to champions
Regulatory, Scientific, HTA advice
3. Repurposing SA. Discussion on proposal, can include relevant stakeholders

STAMP's framework (III)

- The framework was endorsed in the Pharmaceutical Committee the 11th of July, 2019
- A pilot phase to test the proposals was planned to start by March 2020, to learn from the practical applications and to build on the concepts identified in the framework
- A "repurposing observatory group" (RepOG) was going to monitor the progression of the pilot.
- Initially chaired by Spain, supported by NCA and the EMA, includes Champions and Industry representatives

Repurposing observatory group (RepOG)

- The RepOG has to report to the Pharmaceutical Committee and will conclude on practical aspects of the pilot, will report on the challenges, successes and opportunities, and will make recommendations
- Providing contact point for regulatory authorities and other stakeholders
- RepOG not involved in selecting Champions or medicines for the pilot nor any individual assessment or decision making role for the individual pilot projects


Approved indication
Champion awareness
Dissemination activities
Variation, Extension, MAA
Champion proposes new indication
Contact points (EU-IN and EMA)
Interaction with MAHs
Regulatory procedural guidance
RepOG
Champion assembles advised data
Champion assembling supportive data
Regulatory, Scientific, HTA advice

Preparation for the pilot

- In the preparation for launching the pilot by the end of March 2020, the RepOG worked on:
  - Internal circuits (EU-Innovation Network, scientific and regulatory advice structures, others…)
  - Guiding documents (specifically, contact points for different stakeholders, Questions & Answers document, a dissemination plan, submission form, etcetera)
- Public communication was expected before launching

An unprecedented situation

World Health Organization

REMAP-CAP

NIH National Institutes of Health
Turning Discovery Into Health

ACCELERATING COVID-19 THERAPEUTIC INTERVENTIONS AND VACCINES (ACTIV)

RECOVERY
Randomised Evaluation of COVID-19 Therapy

UNIVERSITY OF OXFORD

EMA Endorses Use Of Dexamethasone In COVID-19

The Move Should Speed Up EU National Approvals

18 Sep 2020 | **NEWS**

by Ian Schofield

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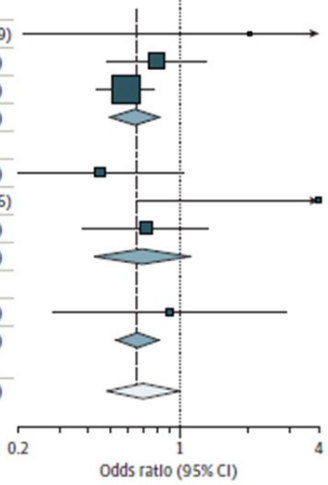
Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect)			222/678	425/1025	0.66 (0.53-0.82)	100.0
$P = .31$ for heterogeneity; $I^2 = 15.6\%$						
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



During the COVID-19…

- We continued meeting on a more or less regular basis
- Lessons learned from COVID-19
  - Dexamethasone case (from the industry perspective and from the regulatory perspective)
  - A survey on the activities of the NCA on repurposing
  - Continuing preparation for the pilot

Proposal for a framework to support not-for-profit organisations and academia in repurposing authorised medicines

Question and Answers on repurposing pilot project

V. 14 February 2020

Questions & Answers

1. What is medicines’ repurposing and why it is important?
2. What is the proposed framework to support repurposing?
3. What is the goal of the medicine repurposing pilot project?
4. Who coordinates the pilot project?
5. Who can apply?
6. Which medicines are eligible?
7. What are the benefits of taking part in the pilot?
8. How will candidate medicines be selected during the pre-entry phase?
9. What are the steps of repurposing pilot?
10. How to apply and what information to submit to enter the repurposing pilot?
11. What happens after the scientific advice?
12. How is the Industry engaged in the repurposing pilot?
13. For how long will the pilot run?
14. What fee will be applied?
15. What information on the selected medicines will be made public?
16. Annex. Contact points in competent authorities and fee-related information

Annex. Contact points (...) and fee info

Institution	Country	Type of advice provided	Fees for informal meetings	Fees for formal meetings	If yes, amount
SÚKL	CZ	Formal and informal	NO	NO	N/A
ANSM	FR	Only formal	NA	NO	N/A
FIMEA	FI	Only formal	NA	YES	5.000 €
AEMPS	ES	Formal and informal	NO	NO	N/A
NIPHN	HU	Formal and informal	NO	NO	b
HPRA	IE	Formal and informal	TBD	TBD	N/A
AIFA	IT	Only informal*	NO	NO	N/A
PEI	DE	Formal and informal	NO	YES	Variable
FAMHP	BE	Only formal	NA	YES	Variable
EMA	EU	Formal	For SA pre-submission meeting	YES *SA fee waiver (TBC)*	Standard fees for SA, taking into account any fee reduction which might be applicable

DRAFT

Repurposing Pilot project for authorised medicines

Submission Form

(To be submitted to: see Annex to the Q&A on repurposing pilot project)

Active substance (s)	

Champion	
Champion[1]	
Contact person details	

New therapeutic use targeted	
New proposed condition/indication	
Is the proposed new condition/indication for the authorised active substance distinct to the currently authorised indication(s) listed in section 4.1 of authorised medicinal product(s) in the EEA?	*Yes/No*
Do you hold an orphan designation for the proposed repurposing project?	

Authorised medicinal product(s) in the EU/EEA	
Authorised indication(s) (section 4.1 SmPC)	*To be listed/summarised*
Authorised pharmaceutical form(s)	*An extract of the Public Data from Article 57 database[2] can be provided as an annex*
Authorisation details (date of first authorisation, MAH name)	*An extract of the Public Data from Article 57 database[2] can be provided as an annex*
Has the innovator / brand leader authorised medicinal product been authorised more than 8 years ago?	*Yes/No/Unknown [If possible, provide, , information e.g. product name / MAH(s), date of authorisation and indicate if authorised by a Member State or the European Commission]*
Is an authorised medicinal product(s)	*Yes/No/Unknown*

[1] If Champions are established outside the European Economic Area (EEA), it is advisable for Champions developing the products to nominate a contact point within the EEA to facilitate communication between the Authorities and such Champions. This contact point may be the same as the Champion, or not. For collaborative group, one contact point should be established to act as champion on behalf of the association/network.

[2] The Article 57 database can be accessed in the following link: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/public-data-article-57-database. It contains all medicines authorised in the European Economic Area (EEA). The Marketing authorisation holders must submit and maintain this information in accordance with European Union (EU) legislation. It can be downloaded as an Excel sheet and filtered by active substance. For further details requested in this section, refer to the following links for centrally authorised medicines (search Medicines) or nationally authorised medicines (visit the websites of the national competent authorities).

Authorised medicinal product(s) in the EU/EEA	
containing the concerned active substance out of basic patent / supplementary protection certificate (SPC) protection, and data and market exclusivity periods?	

Champion characteristics	
Please indicate if you are a Not-for- profit organisation as per the definition in footnote[3]	*Yes/No*
Please indicate if you are a collaborative group[4] (*if yes, please provide the composition of the group*)	*Yes/No*
Please indicate if you are an Academic Institution as per the definition in footnote[5]	*Yes/No*
For academia only[#]	*Yes/No*
Is the entity's seat located in the EU, Iceland, Liechtenstein or Norway?	*Yes/No*
Are you meeting criteria c) of the Annex 'Academia status'	*Yes/No*

[#] Of note: this information is without prejudice of taking part to the repurposing pilot

Applicant's planned route for scientific advice	
National Competent Authority	*Yes/No*
Name of NCA	
EMA	*Yes/No*

[3] 'Non-profit organisation' or 'non-profit legal entity' should be understood as a legal entity which by its legal form is non-profit-making or which has a legal or statutory obligation not to distribute profits to its shareholders or individual members; 'Legal entity' should be understood as any natural person, or any legal person created and recognised as such under national law, Union law or international law, which has legal personality and which may, acting in its own name, exercise rights and be subject to obligations;

[4] Collaborative groups and European Reference Networks (ERNs) should be understood as virtual networks or associations of persons without legal personality involving healthcare providers and researchers across Europe.

[5] 'Academia' or 'Academic sector' should be understood as consisting of public or private higher education establishments awarding academic degrees, public or private non-profit research organisations whose primary mission is to pursue research, and international European interest organisations; 'International European interest organisation' should be understood as an international organisation, the majority of whose members are Member States or associated countries, and whose principal objective is to promote scientific and technological cooperation in Europe.

The following elements are important to evaluate the plausibility and feasibility of an authorized medicines repurposing approach. Boxes contain minimum pieces of information that is needed to assess the proposal but descriptions may not be restricted to those elements. It is highly recommended to provide as much information as possible, including references and annexes (max. limit of 20 pages):

1. Product description & mechanism(s) of action

<Substance type (chemical, biological)/structure, authorised dose and route of administration, reference to official product information of authorised medicines[6] (if available)>

2. Proposed new condition(s)/indication(s)

Please consider as much as possible some or all of the components in the following mock-up which may be relevant to cover in the targeted indication:

<Diagnostic use >or <Preventive> or <Symptomatic, curative or disease modifying (if applicable)> <treatment of> <{severity criteria if applicable}> <{target disease or condition}> in <{age group}> patients < {restrictions to patient population, if applicable}> <{restrictions in terms of therapeutic option or prior therapy, or other restrictions, if applicable}> <in combination with other medicinal products <{list relevant combinations, if applicable}><in monotherapy>

3. Background information on the disease/population targeted and the unmet medical need

a) Prevalence of the disease

b) Impact of the disease on life expectancy/quality of life, given current treatment

c) Disadvantages of current treatment

d) Characteristics of population

4. Claim of major public health interest

Please, provide information on how the new indication may add value from the public health interest point of view

5. Does the product hold sufficient promise to address an unmet medical need?

Please, consider all the following and provide justification for missing information. Different points may have more relevance depending on the specific case (for example, in some cases extensive use in a given indication with proof of efficacy makes less important the completeness of non-clinical data; conversely, completely new uses may discuss more thoroughly plausibility and non-clinical data). Add as much information as possible when available.

a) Plausibility of mechanism of action / proof-of concept data to support the new condition/indication (e.g. chronic vs. short-term use, different posology, different mode of action, different targeted population)

b) Preliminary pre-clinical/clinical data / strength of current evidence to address the unmet medical need

c) Real world data available (post-authorisation studies, registry data, named patient basis, magistral preparation, off-label use)

d) Indication is included in clinical guidelines or other recommendations such as health technology assessment (HTA)

[6] See available information through the article 57 database. Follow the instructions in page 1.

e) Safety profile

f) Evidence supporting safety in the proposed new condition/indication

6. Does the Applicant/Champion consider that further pre-clinical & clinical studies are necessary to demonstrate efficacy and safety in this new indication? If yes, please specify.

Please, discuss here any gap in the development that should be covered by further research

7. Does the Applicant/Champion have resources to conduct additional pre-clinical & clinical studies?

Please, discuss here studies already ongoing or planned to fill the gaps

8. Please provide tabular overviews of the completed/on-going/planned pre-clinical & clinical studies (e.g. study type/objectives, species/strain, mode of administration, doses, number of assays/animals/patients, study duration, outcome variables, GLP/GCP conditions)

9. Regulatory status

a) Previous and planned interactions with regulators

b) Orphan drug designation: Yes/No/planned/non-applicable

<Delete as appropriate. If yes, give details.>

c) Potential for Paediatric-use marketing authorisation (PUMA)

d) Potential for 1-year data exclusivity for a new indication (Article 10(5) of Directive 2001/83/EC)

10. Potential marketing authorisation holder (MAH) or other stakeholder interactions

What contacts /discussions (if any) have you had with a (potential) MAH of the active substance or other stakeholders (e.g. patient organisations, professional associations, research organisations, trade associations).

11. Any points the Applicant/Champion wished to address / expected benefits from the pilot

☐ I agree that my candidate project submission is shared within the regulatory network.

List of Annexes

References

Next steps

- RepOG to finish the Q&A (live document) and submission form
- Dissemination plan to be ready by the time of launching of the pilot
- Pilot to be launched by… the end of September?
- A one-stop-shop (a single e-mail, for example) would be desirable but we are still evaluating its feasibility
- Sharing of proposals within the EU-IN, encourage contact between champions at EU level

Members of STAMP Working Group

Member States (Belgium, The Netherlands, Norway, Spain, Sweden, United Kingdom) and the European Medicines Agency (EMA), Anticancer Fund, European Society of Paediatric Oncology (SIOPE), European Patients' Forum, European Organisation for Rare Diseases (EURORDIS), European Federation of Pharmaceutical Industries and Associations (EFPIA), Medicines for Europe, European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), Association Internationale de la Mutualité (AIM), European Commission representatives

Thank you for four attention

Contact

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