Development of Target Product Profiles for Prevention of preterm birth and Management of Pre-term labour

Technical Appendix

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1. SUMMARY

Target product profiles (TPPs) are a document that describes the minimum and preferred characteristics of a novel therapeutic agent for a particular disease or condition. The Accelerating Innovation for Mothers (AIM) project aims to develop new TPPs for maternal health conditions, in order to spur the development of new medicines for use in the antenatal, intrapartum or postpartum period.

We have developed two new TPPs for novel drugs to prevent and treat pre-eclampsia. To achieve this, we have been guided by an expert advisory group and used a structured process of interviews with expert stakeholders, an international online survey and public consultation to understand and incorporate the views of relevant stakeholders into TPP development.

1.1 TARGET PRODUCT PROFILES

Target product profiles (TPPs) are a well-recognised strategy to promote development of innovative medical products such as devices, diagnostic tests and therapeutics. The World Health Organization (WHO) defines a TPP as a document that describes the minimum and preferred (or optimal) characteristics of a target product, aimed at a particular disease or diseases. They specify the key characteristics that the intervention must address, such as clinical indication, target population, desired efficacy, safety, formulation/presentation, stability and storage. TPPs identify upfront the characteristics a product should take, in order to fulfill a specific, unmet clinical need.

TPPs are an important resource for multiple stakeholders in the research and development (R&D) pathway, including funders, researchers, product developers, manufacturers and regulators. TPPs can guide product developers on the operational characteristics that are required in order to meet end users’ needs, and can help funders set specific targets. TPPs inform R&D strategies for researchers and manufacturers (including the design of clinical trials), help frame product dossiers and streamline communication with regulatory agencies. Importantly, TPP development serves as a consensus-generating process, allowing key stakeholder groups to align around a clear set of product goals. In addition, medicines approved by the FDA that addressed a pre-specified TPP have been linked to more rapid regulatory review. These TPPs have been developed in accordance with WHO’s standard procedures for TPP development, and are based on methods used in recently published TPPs.

A systematic review by Cocco et al identified variations in how different TPPs are developed, though they typically involve an initial scoping phase, drafting a TPP through consultation with key stakeholders, and building consensus on an agreed, final TPP document. TPPs are often ‘living’ documents that are refined or updated over time as new information is available. To guide this work, we developed a research protocol based on the methods described by Lewin et al 2020 on developing TPPs for HIV cures, and that of Ferreyra et al 2020 on diagnostics for Neisseria gonorrhoea. Additionally, the systematic review of TPP methodology in diagnostic tests by Cocco et al informed development of this protocol.
2. METHODS

2.1 Overview

The below activities were conducted in accordance with a study protocol, that was reviewed and approved by the Alfred Ethics Committee for Human Research (project number 108/21) prior to commencement of project activities.

2.2 Initial drafting phase

Existing templates for TPP’s have been published previously by the FDA, WHO, Gates Foundation and others. First, we synthesised a template for development of TPPs within the AIM project informed by these examples. Based on the findings of the AIM project pipeline analysis, development of two TPPs for preterm birth prevention and preterm labour management/treatment were identified as high priorities for TPP development. An initial draft of the two TPPs were written by the AIM project group.

2.3 Expert consultation

We contacted 37 stakeholders from clinical, research, academia, international organizations, funder backgrounds, as well as consumer representatives, with a particular interest on pre-eclampsia and eclampsia. The stakeholders were identified from a database of individuals that have previously participated in WHO maternal and perinatal health guideline development, an AIM project database of topic experts, and other salient clinical, research, advocacy and stakeholder networks. Stakeholders were selected in such a way as to ensure appropriate expertise for the topic of interest, with diversity of gender, geographical and technical expertise.

Stakeholders were initially contacted via email. The goal of these interviews was to seek their input on the first draft of the TPPs, including use-case scenarios, and minimum and preferred characteristics for each TPP domain. Stakeholder interviews were conducted over Zoom, and semi-structured through use of a pre-tested interview guide by the interviewer. Informed consent was obtained prior to all stakeholder interviews. In brief, interviews included discussing the domains of the draft TPP sequentially, asking the interviewee’s views on specific TPP domains relevant to their areas of expertise or interest, and inviting any comments they may have on other domains within the TPP. Their feedback was captured through field notes, with “major” and “minor” issues identified.

Overall, 21 stakeholders provided feedback on both TPPs in interviews that typically lasted 60 minutes. Stakeholders (13 females/8 males) came from Africa, Asia/Pacific, Europe, USA and South America, and included 9 obstetrician/researchers, 1 neonatologists, 2 drug development researchers, 2 midwives, 1 WHO staff member, 2 medicines procurement experts, 1 programs implementer, 1 basic scientist and 2 women with lived experience of pre-eclampsia. One stakeholder, with expertise in international regulatory affairs provided written feedback on both TPPs.
2.4 International stakeholder survey

We conducted an international online stakeholder survey, using the approach described by Pelle et al in their recent TPP development process. This online survey followed the structure of the two draft TPPs and was conducted using Qualtrics. The survey was conducted in parallel to the stakeholder interviews and used the same draft version of the TPP.

The population of interest for the survey was professionals working in the field of maternal and perinatal health. This includes clinicians, researchers, funding agencies, international public organizations, programme implementers, policymakers, representatives of consumer advocacy organizations and other relevant health systems stakeholders. Diverse representation from high-, middle- and low-income countries was sought.

Electronic invitations were be sent to ~300 individuals using the following databases:

- Existing AIM project database of relevant experts, which includes individuals from across the aforementioned sectors.
- Content area experts from the WHO Guideline Development Group on Maternal and Perinatal Health (a database of approximately 300 clinicians, researchers, policymakers and implementers working in maternal and perinatal health internationally)
- The WHO Multi-Country Survey on Maternal and Newborn Health network (an existing network of clinicians, researchers and programme implementers across 29 countries)

Additionally, to increase diversity of participation, we distributed the survey through other clinician-researcher networks of multi-country or multi-centre studies, or other listservs of relevant professional communities or groups, including the Cochrane Pregnancy and Childbirth network. The survey was active for 4 weeks. The study protocol pre-specified a minimum of 25 responses per domain to be adequate to evaluate the degree of consensus.

Overall, 46 responses to the survey were received. Respondents were spread across all WHO geographical regions (AFR 17.4%, AMR 26.1%, EUR 15.72%, SEAR 4.3%, WPR 26.1%, EMR 10.9%). There was a diversity of participants from different fields, including researchers (37.0%), clinicians (such as doctor, midwife or nurse, 39.1%), epidemiologists or public health specialists (4.3%), employees or consultants of national or international NGOs (6.5%), staff of funding agencies (2.2%), employee or consultants of a normative body or civil society organisation (2.2%), staff of a health program or implementing organisation (4.3%) or other (including combined clinician/researchers, 4.3%).

2.5 Public consultation

To gather further feedback, the draft TPPs were made available online for public comment via the Burnet Institute website. Readers were invited to submit comments via email. The public comment period lasted approximately 4 weeks (concurrent with the international online survey) and was disseminated via social media. No responses were received via email through the public consultation.

2.6 Synthesis of findings

The outputs of expert interviews were summarised, with key themes and “major” or “minor” concerns identified. The results of the international online survey were analysed and areas where consensus was
not reached (agreement <75%) are discussed below. These inputs guided the subsequent revisions to the TPPs.

3. RESULTS

3.1 Expert interview results

Results from the expert stakeholder interviews showed strong agreement across almost all variables in both TPPs. Major themes identified across both TPPs was the definition of the target population. In the TPP for medicines to prevent preterm birth, many interviewees raised concerns with the broad definition of the target population. There was general confusion as to whether all forms of preterm birth (i.e. spontaneous, PPROM and provider-initiated) were being targeted and whether one drug was proposed to prevent preterm birth in all these situations. Many interviewees highlighted the need to include a more precise definition of the target population.

In the TPP for medicines to treat spontaneous preterm labour, many interviewees did not agree with the definition of the target population as women <34 weeks’ gestation in spontaneous preterm labour. It was suggested that women <37 weeks’ gestation would be a more appropriate target population for tocolytics to manage preterm labour. The initial draft of the TPP used <34 weeks’ gestation, as this is the population that WHO recommends be treated with antenatal corticosteroids (ACS), to mature the fetal lungs in preparation for preterm birth. Tocolytics are used in many situations in order to allow for the administration of ACS to women in spontaneous preterm labour. However, as many interviewees pointed out, many women at risk of late preterm delivery (34-37 weeks’ gestation) are still given ACS, as the evidence for ACS to improve newborn outcomes in late preterm is not clear. In addition, tocolytics are also given to women in spontaneous preterm labour to allow for the transport of women to the appropriate care facility. Finally, stakeholders with experience in low resource settings identified that it is not always possible to determine whether a women is preterm or late preterm. For these reasons many stakeholders suggested all preterm deliveries be included in the target population (<37 weeks’ gestation).

A minor issue that was identified was that the minimum acceptable level of treatment discontinuation (<35%) was too high.

A major issue identified across both TPPs was whether evidence of clinical efficacy in improving neonatal outcomes should be included as a minimum requirement, rather than just a preferred requirement. Some interviewees stated that this must be considered the minimum requirement for a candidate medicine to be used widely. However, other interviewees agreed that clinical efficacy in improving neonatal outcomes was acceptable as a preferred requirement, given the difficulty in powering trials to demonstrated improved neonatal outcomes. These stakeholders agreed that evidence of reduced incidence of preterm birth (prevention TPP) and evidence of a clinically important difference in extending pregnancy duration (treatment TPP) were appropriate as a minimum requirement for new medicines.

In both TPPs, a minor issue that was identified was whether lactating women should be included in the safety profile. Some interviewees suggested that this was not relevant as these medicines would be given to women before giving birth. However, many stakeholders agreed that lactating women should be included, as medicines with a long half-life may prevent breastfeeding immediately after birth. Many interviewees, particularly those with experience in LMICs identified that protecting breastfeeding is vital to women living in LMICs. It was also pointed out that many pregnant women are still breastfeeding their
other infant. Another minor issue identified was that in both TPPs, vaginal administration should be included as a non-invasive administration route.

3.2 Survey results

The results from the survey demonstrate agreement (<75%) across almost all of the variables in both TPPs (Figure 1). In the TPP for drugs to prevent preterm birth, agreement was less than 75% for the minimum requirements for treatment adherence (20% disagree or strongly disagree). In the TPP for drugs to treat spontaneous preterm labour, agreement was less than 75% for the preferred requirements WHO pre-qualification (29% neutral responses, 0% disagree or strongly disagree).
Figure 1. Survey responses

Results from international stakeholder survey. Percentage of respondents that strongly agreed (dark green), agreed (light green), were neutral (grey), disagreed (orange) or strongly disagreed (red) in response to the minimum and preferred variable in the TPP for new drugs to prevent preterm birth (A, B) and treat preterm labour (C, D). Consensus was considered agreement greater than 75% (black dotted line).
4. REFERENCES