DRAFT OUTLINE
Updated for November 2022 Design Lab

Core Protocol for the Predictive Outcomes Platform

Background

The design and implementation of Predictive Outcomes Platform (POP) will be guided by a "Core Protocol," the structure of which will be loosely adapted from rapidly evolving concepts associated with Master Protocols for adaptive platform clinical trials (1-3) and adaptive point-of-care platforms conducted in real-world closed clinical settings (4-6).

Master protocols have been proposed as an efficient clinical trial design strategy to evaluate the efficacy and safety of novel drugs. (7)

The first distinctive feature of this design strategy is to conceive from the beginning a collection of prospective trials, or sub-studies, that share key design and operational aspects. This strategy can evaluate a single therapy across multiple diseases or disease subtypes (basket trial) or multiple therapies for a single disease or indication (umbrella study). In addition, in a platform trial, multiple therapies and their combinations, all for the same disease or indication, can be dropped or added over time, on the basis of accumulating evidence and emergence of novel candidate therapies and biomarkers.

The second distinctive feature is the creation of a perpetual infrastructure designed as a learning system. This infrastructure, also called the platform, includes a well-established, but possibly evolving, network of centers/sites enrolling participants, coupled with a single system to centralize, manage, and analyze individual participant data.

This approach has been used to generate randomized evidence to support the approval of drugs, as well as real-world comparative effectiveness evidence supporting the value proposition of therapies and reimbursement discussions.

The high-level and specific objectives, study schema, design, and statistical aspects are specified in a written master protocol document and sub-protocol documents. Multiple stakeholder groups develop and review these protocol documents, including investigators, developers of the investigational medical product, patients, and regulatory agencies.

A new class of master protocols for predictive outcomes platform studies

Building on the design strategy of master protocols, we propose to adapt the general framework of master protocols for POPs as a design strategy for multiple sub-studies to identify and predict which patients will respond to specific drugs/drug classes, all within the same overall study infrastructure.

The main similarities between master protocols for clinical trials and a core protocol for a POP are:

Commented [GH1]: Question to Team: Should we consider splitting off the first 2 pages and expanding/developing it into a white paper? The focus could be on advancing from one-off studies to a scalable predictive modeling platform, and the potential role for a Core Protocol in this transition process?

Commented [GH2]: Team: Do we want to frame POP as a "study infrastructure"? Perhaps a modeling infrastructure??

1) Devising, from the beginning, a collection of studies with the common high-level objectives of predictive model for response to a single therapy across multiple diseases or for multiple therapies for one disease, and
2) Creating a perpetual infrastructure designed as a learning system instead of a one-off model

There are also a few key differences:

1) Whereas master protocols for clinical trials focus on the evaluation of drugs, core protocols for a POP focus on the evaluation and predictive value of heterogenous patient responses to a class of drugs (e.g., immune checkpoint inhibitors).
2) Whereas master protocols for clinical trials involve prospective collection of data, the evaluation of predictive outcomes will rely primarily on secondary use of health data. In a POP, the platform consists of a network of real-world data providers. Data sources can be added over time, including, for example, multiple EHR data providers, insurance claims, disease registries, and patient generated health data (e.g., mhealth and mobile device data, patient reported outcomes). Finally, the platform will rely on aggregating evidence, rather than individual participant data, across the distributed network of data and analysis partners.
3) The POP will be deployed in the "downstream" or post-marketing space. The LEAPS Project emphasizes the importance of generating evidence that is fit-for-purpose for patient-centered decisions/actions by key stakeholders. As such, core protocols for a POP will rely heavily on input from payers, providers, patients, and developers into the technical design and implementation specifications.
4) Building on 3), a POP will be designed and implemented in close coordination with a distributed platform for advancing innovations in value-based contracting, or "Precision Reimbursement." (8) (*see Figure 1).*

Our aim is to offer general guidance for developing the written content of a core protocol and sub-protocols for a POP. We illustrate the design strategy with an initial case study being evaluated in the NEWDIGS LEAPS Project focused on improving our ability to predict which patients with metastatic non-small cell lung cancer (NSCLC) will benefit from immune checkpoint inhibitors.

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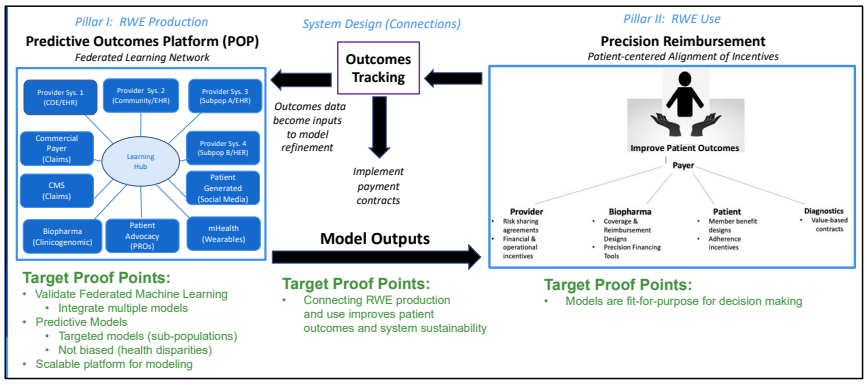

Fig. 1: Overview of the LEAPS downstream system design module intended support the coordinated evolution of next generation RWE platforms and value-based reimbursement models. Evidence from POP informs Precision Reimbursement contract designs, while the payment models incentivize and reward platform-based RWE production. Both are essential to each other, and to advancing the knowledge, practice, and sustainability of Precision Medicine.

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Core Protocol Outline

I. Platform Design

- Introduction
- Plan
  - Defining the question
  - Mapping stakeholders
  - Defining the metrics
- Produce
  - Analytics
    - Generating the models (inventory of methods, strengths/weaknesses)
    - Integrating the models (inventory of methods, strengths/weaknesses)
      - The first methodology we will explore for model integration is Federated Learning models
      - Inventory of Federated Learning methods, strengths/weaknesses)
    - Iterative refinement process
  - Data
    - Data Types/Characteristics
    - Data Assessment & Risk Engineering Framework (DARE)
    - Data Dictionary
  - Management (Learning Hub and its infrastructure)

Commented [GH3]: TEAM: This section focuses on processes and infrastructure — things that are generalizable, scalable, and case-agnostic.

Commented [GH4]: TEAM: Are variables in Data Dictionary case-specific or generalizable, of combination of both?

- Governance (e.g., information sharing, IP, decision making, ethics, contractual agreements with POP network partners, etc.)
- Processes for managing the evolving models (?curation, archiving)
- Technologies (e.g., trusted server)
- Other shared enabling resources? (ontologies; other??)
- Human capital/expertise

- Use
  - Model Assessment (metrics, thresholds)
  - Dissemination, communication, sharing of models with decision-makers?

Commented [GH5]: TEAM: Is this out of scope of Core Protocol?

II. Appendix A – Case Studies

Case Study #1: Advanced NSCLC & ICIs

- Plan
  - Question(s)
  - Stakeholders
  - Metrics (outcome & impacts)
- Produce
  a. Analytics
    - Generating the models (selected methods, rationale)
    - Integration of models (selected methods, rationale)
    - Iterative refinement process (specific steps)
    - Coding algorithms?

  b. Data
    - Data portfolio strategy (what types) and rationale
    - Specific data sources selected?
    - Data Dictionary (case-specific variables?)
    - Data management requirements at the sites??

  - Learning Hub
    a. Governance
    b. Management of the models that are shared
    c. Trusted server – protocols, processes, transparency/communications
    d. Expertise (case-specific; other technical; functional/stakeholder-specific)
- Use
  - Assessment of models by stakeholder decision-makers
  - Dissemination/communication to stakeholder decision-makers

Commented [GH6]: TEAM: Do we list/profile each Network Partner and their data characteristics in Appendix B, and just list the ones being used for this case study here? The POP Network then would be a sustainable infrastructure, with selected partners engaged for different case studies over time.

Case Study #2: TBD

III. Appendix B: Data Sources or POP Network Partners?

Commented [GH7]: TEAM: Are specific network partners and their data profiled here? Are they part of the infrastructure & we just add new ones as they join?

References

1. Alexander BM, Ba S, Berger MS, Berry DA, Cavenee WK, Chang SM, et al. Adaptive Global Innovative Learning Environment for Glioblastoma: GBM AGILE. Clin Cancer Res. 2018;24(4):737-43.

2. Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther. 2009;86(1):97-100.

3. Pancreatic Cancer Action Network. Precision Promise [Available from: https://www.pancan.org/research/precision-promise/.

4. Angus DC, Berry S, Lewis RJ, Al-Beidh F, Arabi Y, van Bentum-Puijk W, et al. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study. Rationale and Design. Ann Am Thorac Soc. 2020;17(7):879-91.

5. Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) [Available from: https://clinicaltrials.gov/ct2/show/NCT02735707.

6. REMAP-CAP response to the COVID-19 pandemic [Available from: https://www.remapcap.org/coronavirus.

7. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med. 2017;377(1):62-70.

8. Eichler HG, Trusheim M, Schwarzer-Daum B, Larholt K, Zeitlinger M, Brunninger M, et al. Precision Reimbursement for Precision Medicine: Using Real-World Evidence to Evolve From Trial-and-Project to Track-and-Pay to Learn-and-Predict. Clin Pharmacol Ther. 2022;111(1):52-62.