Drivers of Variability Exploration (DiVE!):

A Review to Inform A Proposed Observational Study Evidence Synthesis and Reporting Checklist

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BACKGROUND

- Literature reviews involving the synthesis of natural history or burden of illness (BOI) data for rare and/or clinically heterogeneous diseases can be challenging, as there are often insufficient standardized data to permit formal meta-analysis.[1]
  - Examples of challenges include small sample sizes (e.g., only data from case reports available), variation in ascertainment of the disease or outcomes of interest (e.g., the data available are identified using patient charts versus claims dataset, or roadblocks to prospective data collection), missing data (e.g., patient lost to follow-up).
- Evidence syntheses that lack formal meta-analysis are often described as being narrative; and without clearly-outlined methods, particularly for summarizing quantitative data.[2]

OBJECTIVE

To identify synthesis and reporting guidelines, for topics where a formal meta-analysis would be inappropriate.

METHODS

1. **Targeted review** — Published guidelines were identified in PubMed and Google Scholar
2. **Guideline summaries** — Guidelines were reviewed; Key steps and considerations for evidence synthesis were summarized
3. **Checklist** — Gaps were identified with respect to synthesizing data from natural history and BOI studies; Strategies to address the identified gaps were developed

RESULTS

- One identified guideline described approaches for synthesizing and reporting treatment data when meta-analysis is not possible.[3]

Key components outlined in identified guideline:
1) Grouping studies for synthesis
2) Prioritizing results for synthesis
3) Handling heterogeneity and assessing certainty of findings
4) Data presentation/reporting

- While thorough, the guidance was limited to methods for synthesizing treatment effects from a relatively homogenous group of interventional studies.

Guidance for characterizing drivers of variability, or methods for synthesizing data from observational studies with heterogeneity in study design and populations, was not available.

Building from the existing guideline, a checklist was developed outlining an iterative approach for synthesizing natural history and BOI data comprising (**Figure 1**):

1) Conceptual model development to inform PECOS (Population, Exposure, Comparators, Study design) criteria
2) Initial review and subsequent grouping of data systematically identified, with prioritization for synthesis
3) A reporting structure for characterizing drivers of variability in tabular and narrative forms
4) Effective data visualization

Figure 1: DiVE! CHECKLIST

1) Conceptual model

Conduct preliminary literature review to inform PECOS:
- Assess the relationships between potential exposures and outcomes of interest
- Identify published literature reviews on same/similar research topic
- Identify changes in clinical practice

For rare diseases, in particular, consider the implications of broadening the target population versus missing data by keeping it more specific
- Consider consultation with clinicians on appropriate proxy diseases

2) Grouping of data

Conduct preliminary data extraction to assess breadth and heterogeneity in the identified evidence base for each outcome:
- Overall number of studies may be large but the amount of robust data available for each outcome may be sparse
- May need to prioritize certain outcomes in synthesis/dissemination; discuss with key stakeholders prior to full data extraction

Create overarching groupings – informed by clinical guidelines, expert opinion, previous review, or a pivotal study:
- Organize disparate data by overarching categories according to outcome, population, exposure, timepoint
- Determine whether author-reported definitions could be grouped into broader categories
- Use groupings to organize data extraction sheet for ease of creating summary tables

3) Reporting structure for characterizing drivers of variability

Split up large summary tables into smaller tables; utilize groupings

Summarize range of estimates within comparable samples, and/or at comparable timepoints, for each outcome grouping; as well as key drivers of variability reported within and across studies
- Determine if any high burden or other notable patient subgroups emerge

Provide key takeaways for each outcome grouping and for trends across the identified evidence base (e.g., overview of disease progression across multiple outcomes)
- Identify more recent and robust studies to use as guide for reporting on variability and high-level trends across evidence base

4) Effective data visualization

Create data visualizations to highlight trends across evidence base as well as key drivers of variability
- E.g., dynamic data visualization
- Prioritize studies for the visualization (e.g., based on sample size or from those reporting on multiple outcomes of interest)
- Utilize groupings and consider a feature to select individual groups for viewing data summaries, separately or overall

DISCUSSION

- The breadth and heterogeneity of the included data, and resulting scope of the synthesis and reporting, can be difficult to determine *a priori* for literature reviews of observational data.
- Therefore, it is important to start to conceptualize the synthesis and reporting as early as possible; not waiting until extraction of all data that meets the PECOS criteria as specified in the protocol.
- Check-ins with stakeholders at various stages of the literature review process (e.g., at preliminary data extraction step, after synthesis is completed for each outcome) are also important to align on strategies to focus the evidence base, plan for results dissemination, and to discuss high-level key findings.
- Insights from clinical experts may also be important for interpreting disparate data.

CONCLUSION

- Synthesis methods that consider the wider evidence base, rather than estimating a central tendency, are valuable to understand drivers of heterogeneity in observational study data.
- The proposed checklist may be implemented for synthesizing natural history data, and characterizing components of disease burden.

REFERENCES

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