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# Planning Phase 3 Clinical Trials More Efficiently Using An Evidence-Mapping Approach

Rutherford L[1], Ahdesmäki O[1], Clarke N[1], Martin A[1], Witkowski M[1]

[1] Crystallise Ltd, Stanford le Hope, Essex, UK

## Objectives:

- A new technology is required to be compared directly and indirectly to standard care to achieve HTA approval, which usually requires conducting a network meta-analysis (NMA).
- This can be facilitated by designing phase 2 and 3 trials to include comparators and outcomes that will both best differentiate the new product and allow it to be compared with likely standard of care at the time of submission across a number of countries.
- Conducting a full systematic review and NMA to provide a definitive answer is costly and time consuming and may not be justified early in a product's development. However, using only data from trials known to the manufacturer risks missing key studies.
- We propose an efficient and accurate method of identifying likely NMA networks using data only from abstracts of published research papers identified by a comprehensive and systematic search, to quickly and affordably assist in planning a phase 3 clinical trial.

## Methodology:

- A recent systematic literature review (SLR) with NMA comparing efficacy and safety of two antiretroviral therapies for HIV was used as the gold standard[1].
- Using an Evidence Mapper tool (www.evidencemapper.co.uk), abstracts from the 206 studies included in the SLR were indexed by fields including each treatment comparison, trial name and reported outcomes.
- A network-feasibility tool assessed the possibility of creating a connected network for a hypothetical new drug that would include efavirenz as a key comparator.

## Results:

- The Mapper allowed an easy determination of the most commonly-assessed interventions and outcomes per trial. Viral suppression at 48 and 96 weeks, CD4 cell count at 48 and 96 weeks, discontinuations and treatment-related adverse event rates were the most commonly-reported outcomes.
- The Mapper sensitivity for predicting the network for these outcomes was 73% to 100% and specificity was 50% to 100% (Figure 1).
- For a new technology to be compared indirectly to efavirenz for the six most common outcomes, its trial comparator could be atazanavir/ritonavir, doravirine, darunavir/ritonavir, dolutegravir, lopinavir/ritonavir, nevirapine, raltegravir or rilpivirine. However, the strongest network for these outcomes would exist where raltegravir, rilpivirine or dolutegravir were the direct comparators for the new drug (Figure 3, 4).

| Outcome | Discontinuations | Viral suppression 96 wk | Viral suppression 48 wk | Viral suppression 12 wk | CD4 count 96 wk | CD4 count 48 wk | CD4 count 24 wk | TEAE | TE SAE | Weight change 48 wk |
|---|---|---|---|---|---|---|---|---|---|---|
| Sensitivity | 100% | 92% | 92% | 25% | 73% | 83% | 45% | 92% | 100% | 67% |
| Specificity | 100% | 100% | - | 100% | 50% | 100% | 100% | 100% | 100% | 80% |

Fig 1. Sensitivity and specificity of the Evidence Mapper predictions compared with outcomes that were included in full NMA[1] TEAE treatment-related adverse events; TE SAE Treatment-related severe adverse events; wk weeks

| | 1. CD4 cell count W48 | 2. CD4 cell count W96 | 3. Discontinuations due to AEs | 4. Treatment-related AEs | 5. Viral suppression W48 | 6. Viral suppression W96 |
|---|---|---|---|---|---|---|
| EFV vs LPV/RTV | 1 | 0 | 2 | 0 | 3 | 1 |
| EFV vs NVP | 2 | 0 | 1 | 1 | 4 | 1 |
| Efavirenz vs Raltegravir | 1 | 0 | 0 | 0 | 1 | 0 |
| EFV vs RAL | 1 | 2 | 4 | 7 | 4 | 3 |
| EFV vs RPV | 0 | 1 | 6 | 1 | 4 | 1 |
| EFV vs TMC278 | 1 | 0 | 1 | 1 | 1 | 0 |
| EFV vs ZDV | 0 | 0 | 0 | 1 | 0 | 1 |
| FTC/NVP vs LPV/RTV | 0 | 0 | 0 | 1 | 0 | 1 |

Fig 2. Section of Evidence Map showing comparison of interventions against six different outcomes as indexed from abstracts

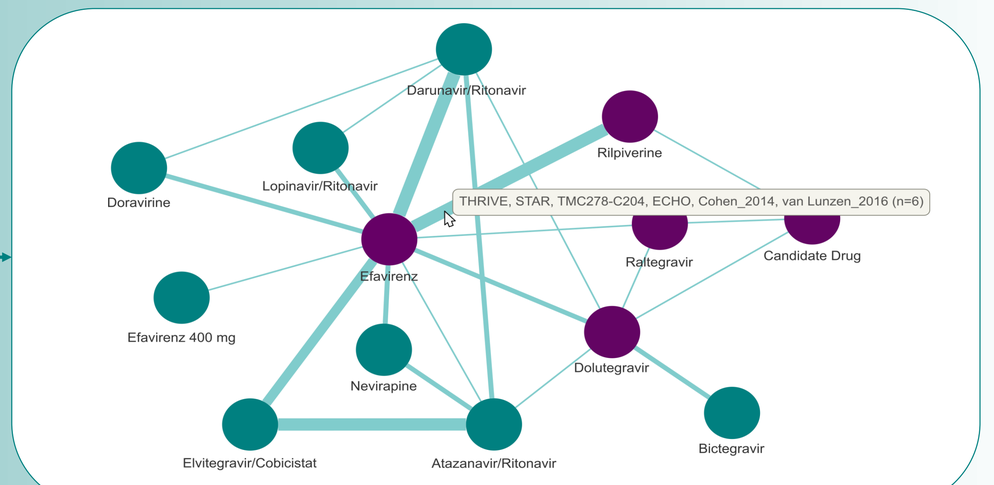


Fig 3. Network map showing comparison of existing interventions and candidate drug against discontinuations due to adverse events

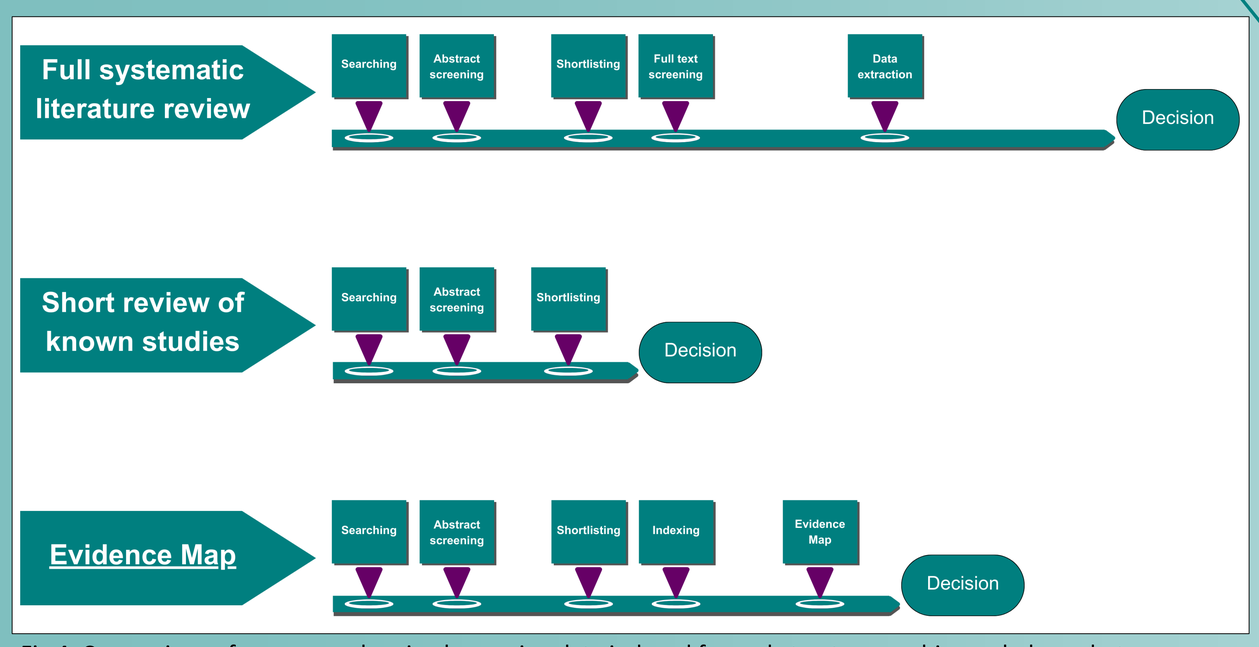


Fig 4. Comparison of processes showing how using data indexed from abstracts can achieve a balance between efficiency and accuracy when planning comparisons within a phase 3 clinical trial

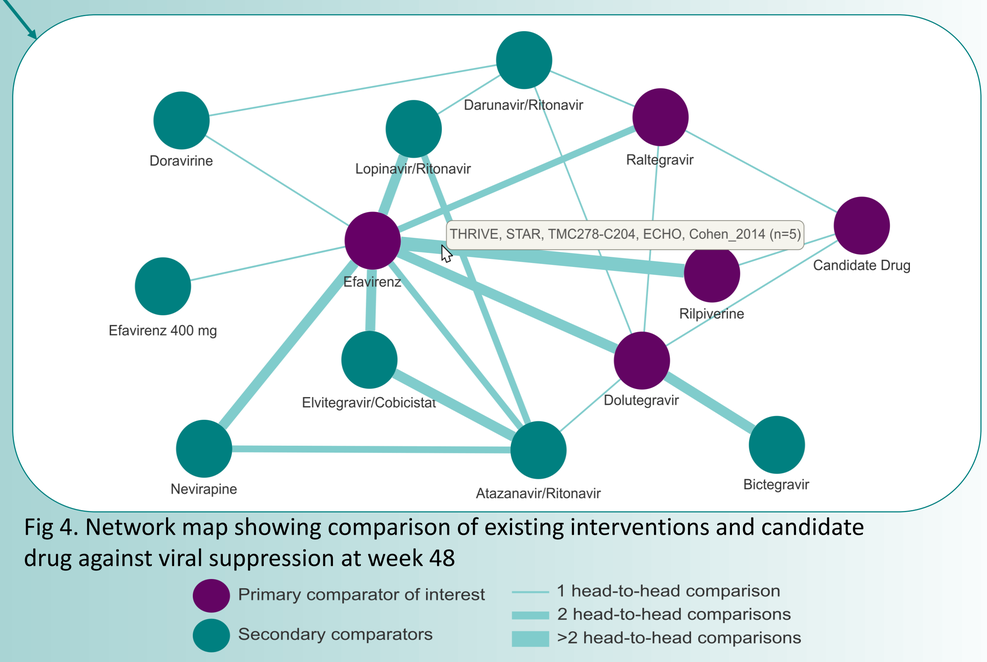


Fig 4. Network map showing comparison of existing interventions and candidate drug against viral suppression at week 48

## Conclusions:

- A network was created for common outcomes using data indexed only from abstracts of relevant publications, with a high accuracy compared with a full NMA.
- This method can be used to efficiently plan a phase 3 clinical trial to best support direct and indirect comparisons with the most important existing technologies.
- The results are comprehensive due to the systematic search but are available much more rapidly and affordably than with a full SLR and NMA.

1. Kanters, S. et al. EClinicalMedicine 28 (2020) 100573

**Crystallise Ltd:** https://www.crystallise.com/

**Evidence Mapper:** https://www.evidencemapper.co.uk/

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**Email us at:**
contact@crystallise.com