

Living network meta-analysis : Improving evidence synthesis and beyond

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Do the current systematic reviews address the needs of patients, physicians and decision makers ?

- A systematic review typically focuses on the comparison of two treatments (A versus B , or A versus Placebo)
- The key question posed by patients, physicians and decision makers: **Among all available treatments for a given disease , which interventions work best?**
- To this end, reviews should ideally incorporate
 - 1) all treatments available for the condition of interest
 - 2) all clinical trials assessing these treatments.
- To assess the randomized evidence not covered by SRs , we performed a study in the field of lung cancer

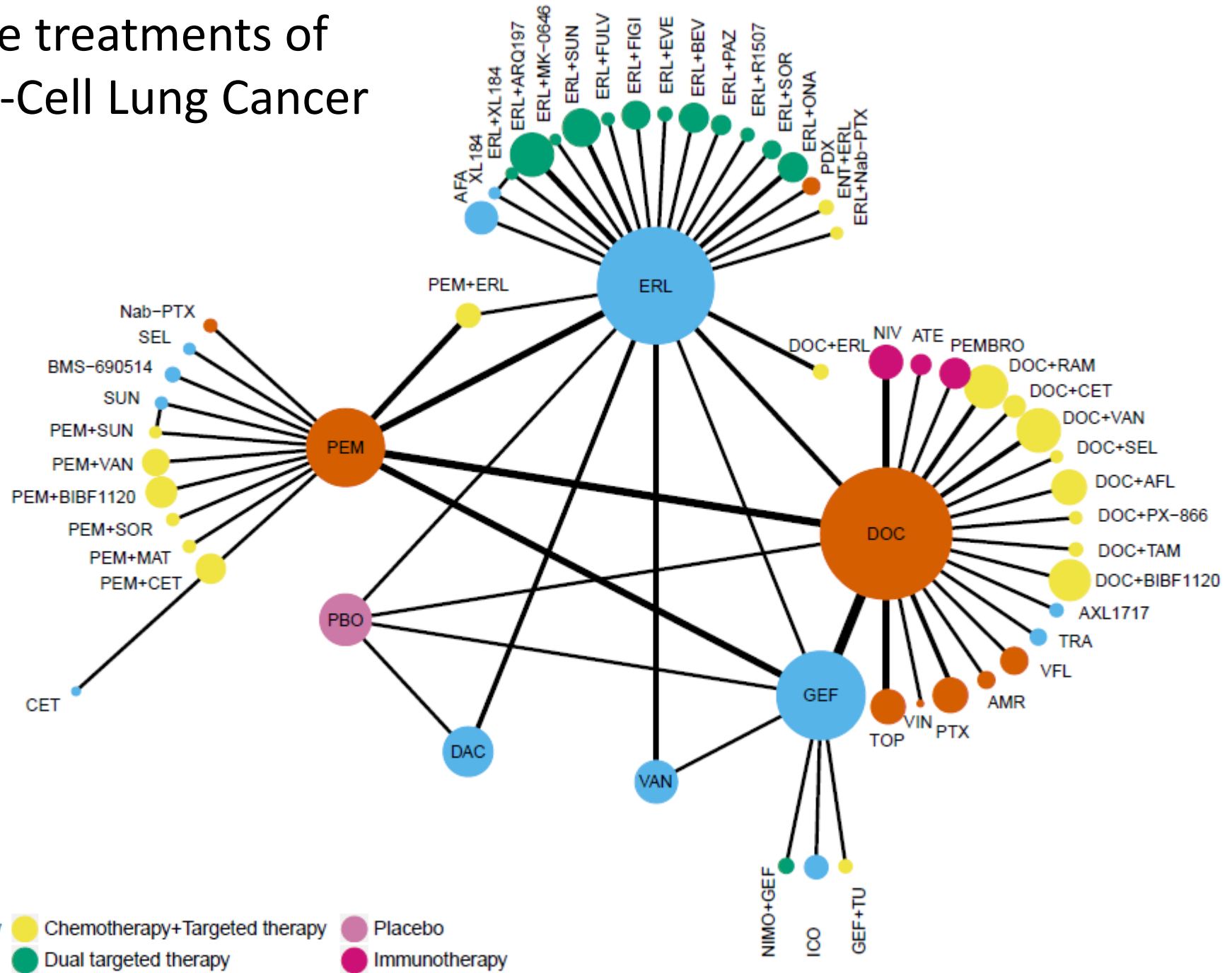
Randomized evidence not covered by SRs : The example of **second-line treatments of advanced non-small-cell lung cancer**

- Comprehensive strategy to identify
 - all RCTs, with published and unpublished results
 - all SRs that addressed at least one comparison between the treatments available
- From 2009 to 2015, for each year
 - We constructed **cumulative networks of randomized evidence**
 - **We evaluated the amount of evidence missing from SRs published in comparison to the total randomized evidence available at each time with the proportion of missing**
 - **trials**
 - **patients**
 - **treatments**
 - **treatment comparisons**

Example of 2nd line treatments of advanced Non-Small-Cell Lung Cancer

Treatments (n=58)
 Trials (n =92)
 Patients (n=32 434)

29 Systematic reviews



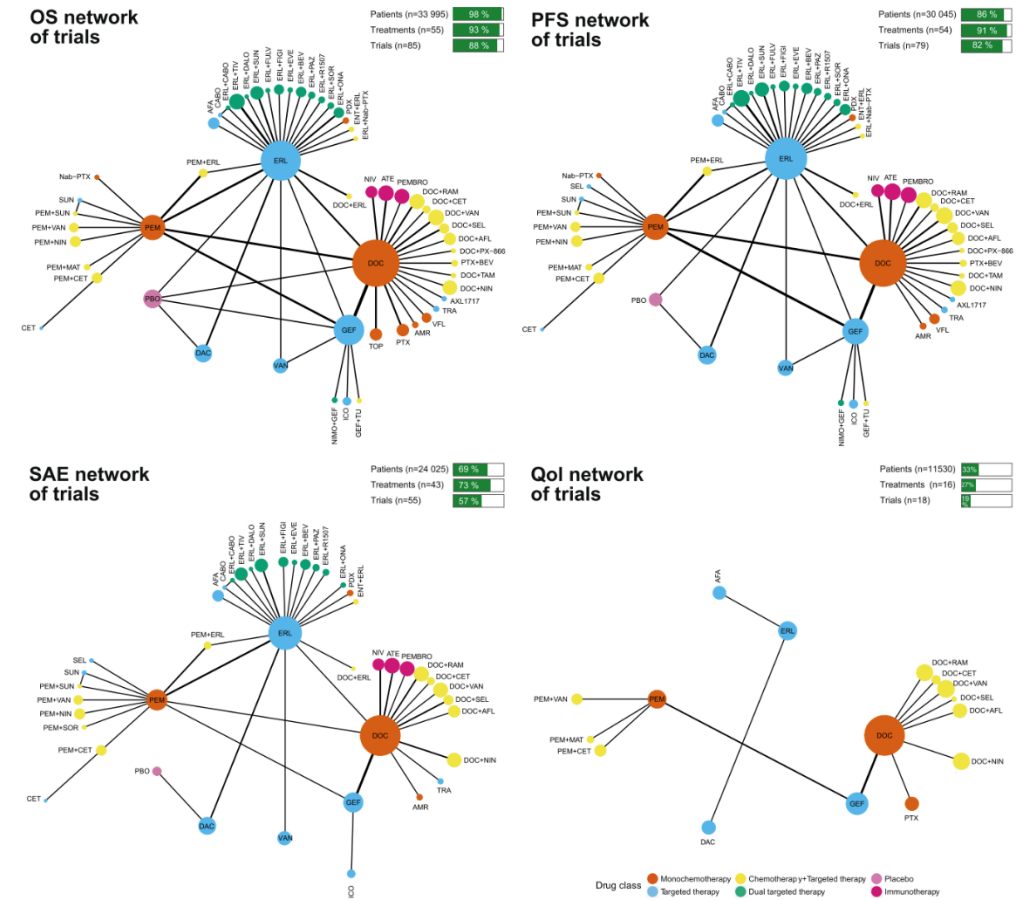
The failure of the current systematic reviews system

- Even when considered collectively, the series of existing systematic reviews does not provide a complete and up-to-date synthesis of evidence for a given condition.
- The current process leads to a series of disparate systematic reviews in terms of selection criteria, search dates, methodological quality
- Furthermore, the scope of these SRs is frequently overlapping.
- The overall systematic review system is not efficient

The evidence synthesis process is also affected by the poor quality of primary research

- Systematic Reviewers are frequently complaining about the poor quality and transparency of primary research
 - Half of completed RCTs are not published
 - 40% of published trials are at high Risk of Bias
 - Incomplete reporting and selective reporting are frequent
 - Important outcomes are frequently missing

Therefore, we may wonder if we should rethink the Evidence Synthesis ecosystem

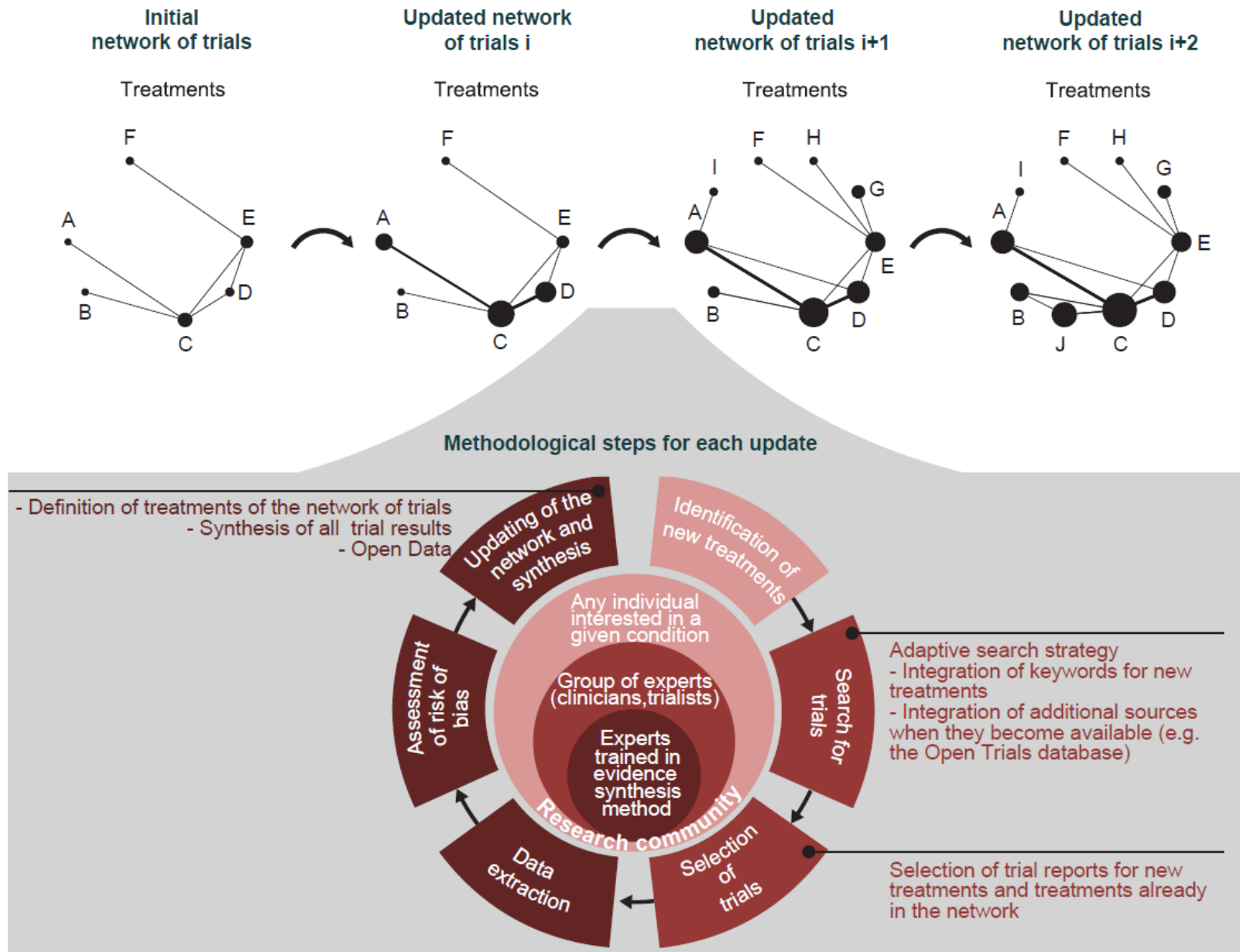


From a series of meta-analyses to a live cumulative (or living) network meta-analysis

- We propose switching :
 - **from a series of disparate systematic reviews and meta-analyses**, which are frequently out-of-date and redundant,
 - **to a single systematic review and evidence synthesis** (including MAs and NMAs) **of all available treatments, continuously updated for a specific condition or therapeutic indication (living NMA)**

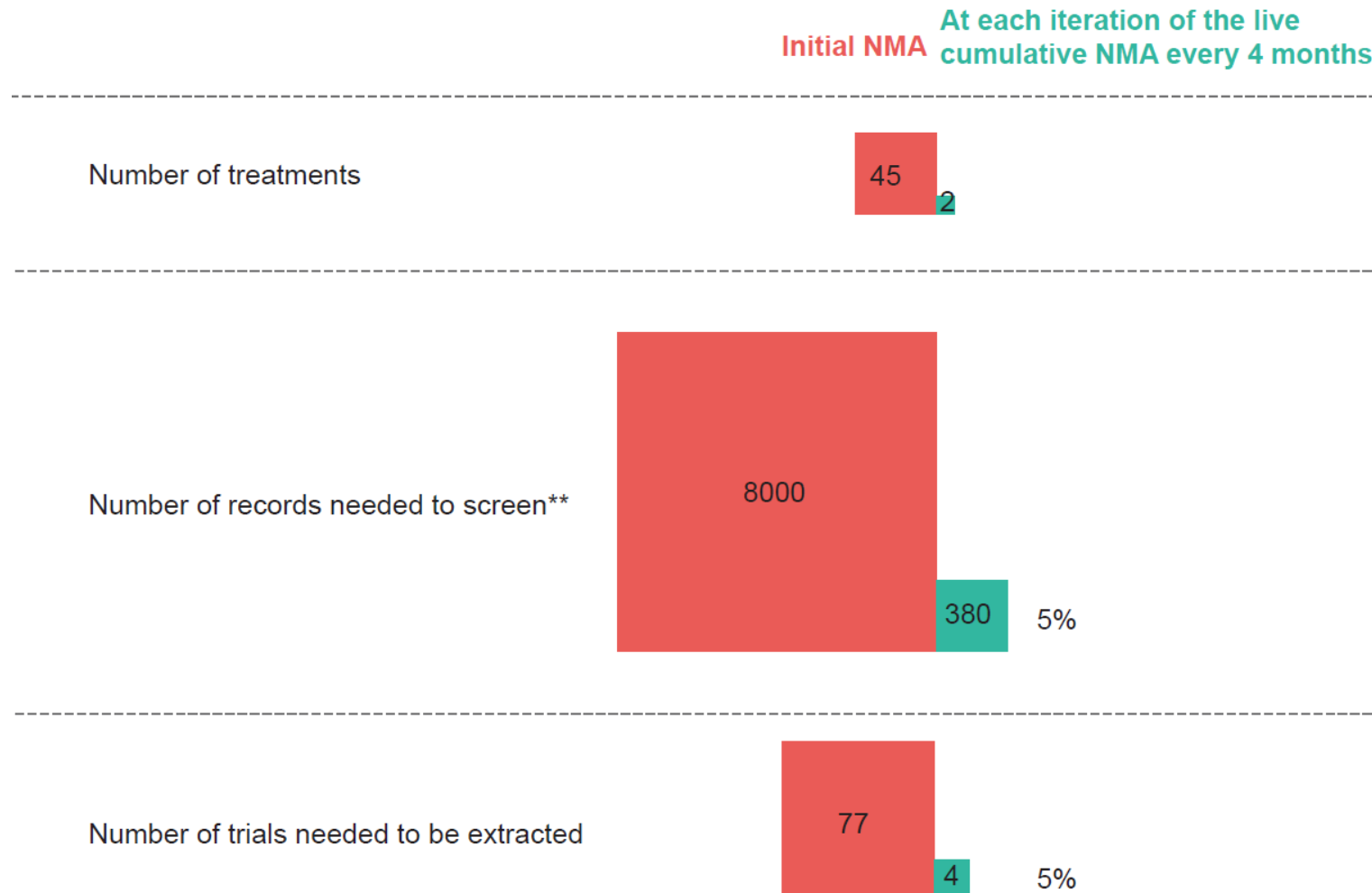
(Crequit, BMC Medicine 2016)

Living network meta-analysis



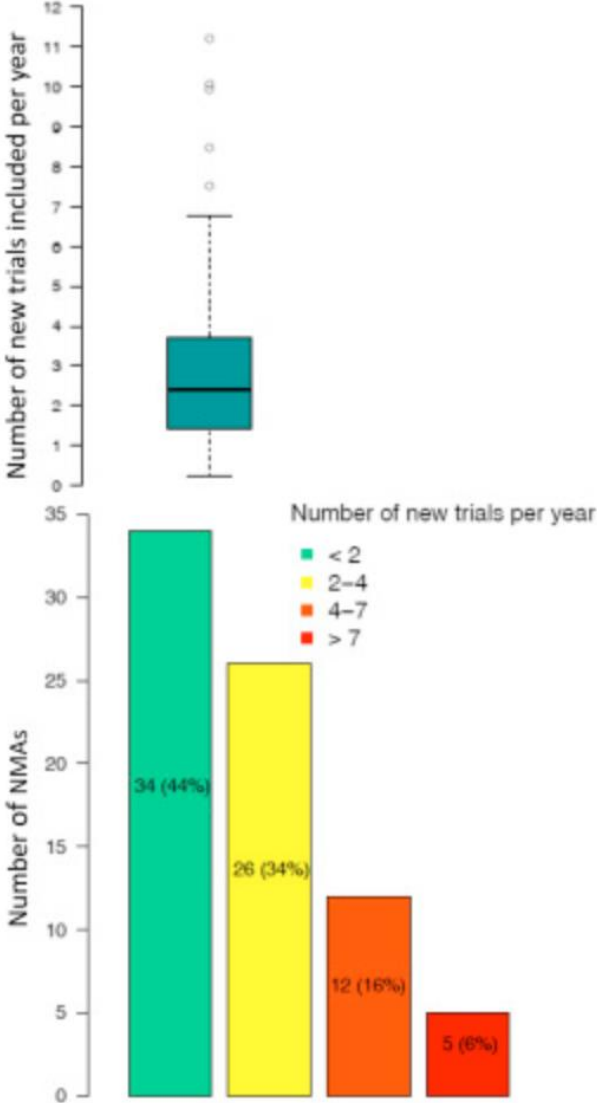
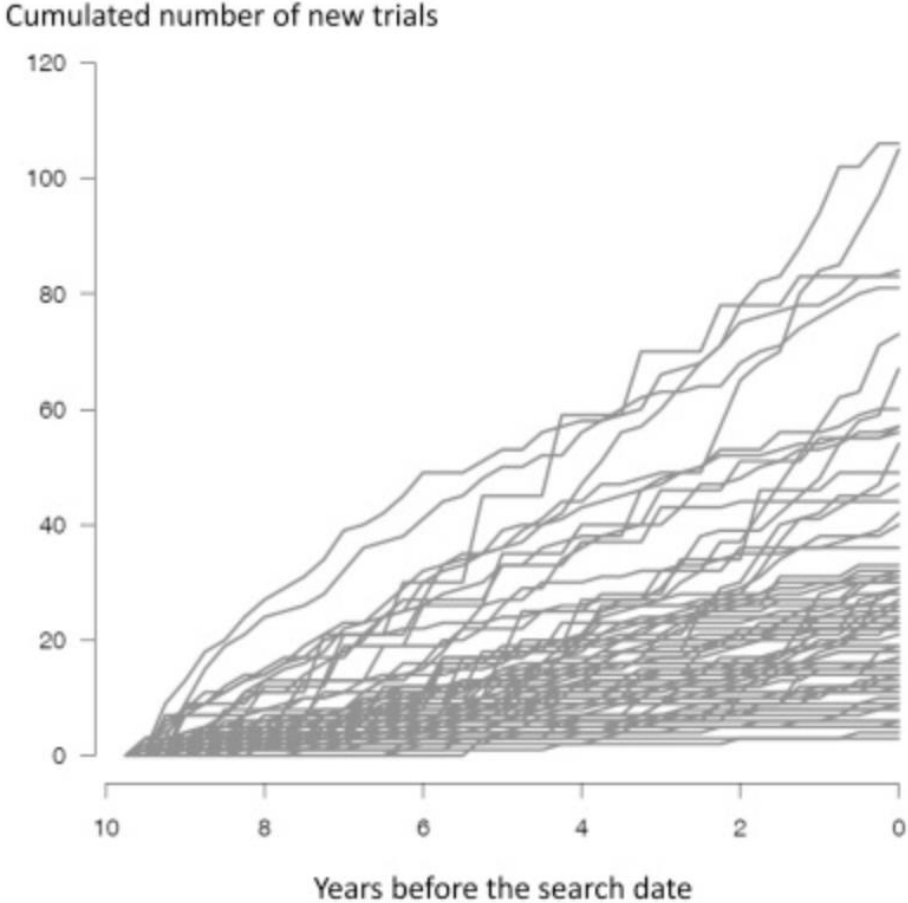
(Crequit, BMJ Open 2016)

Work-load of living NMA for 2nd line treatments of advanced NSCLC



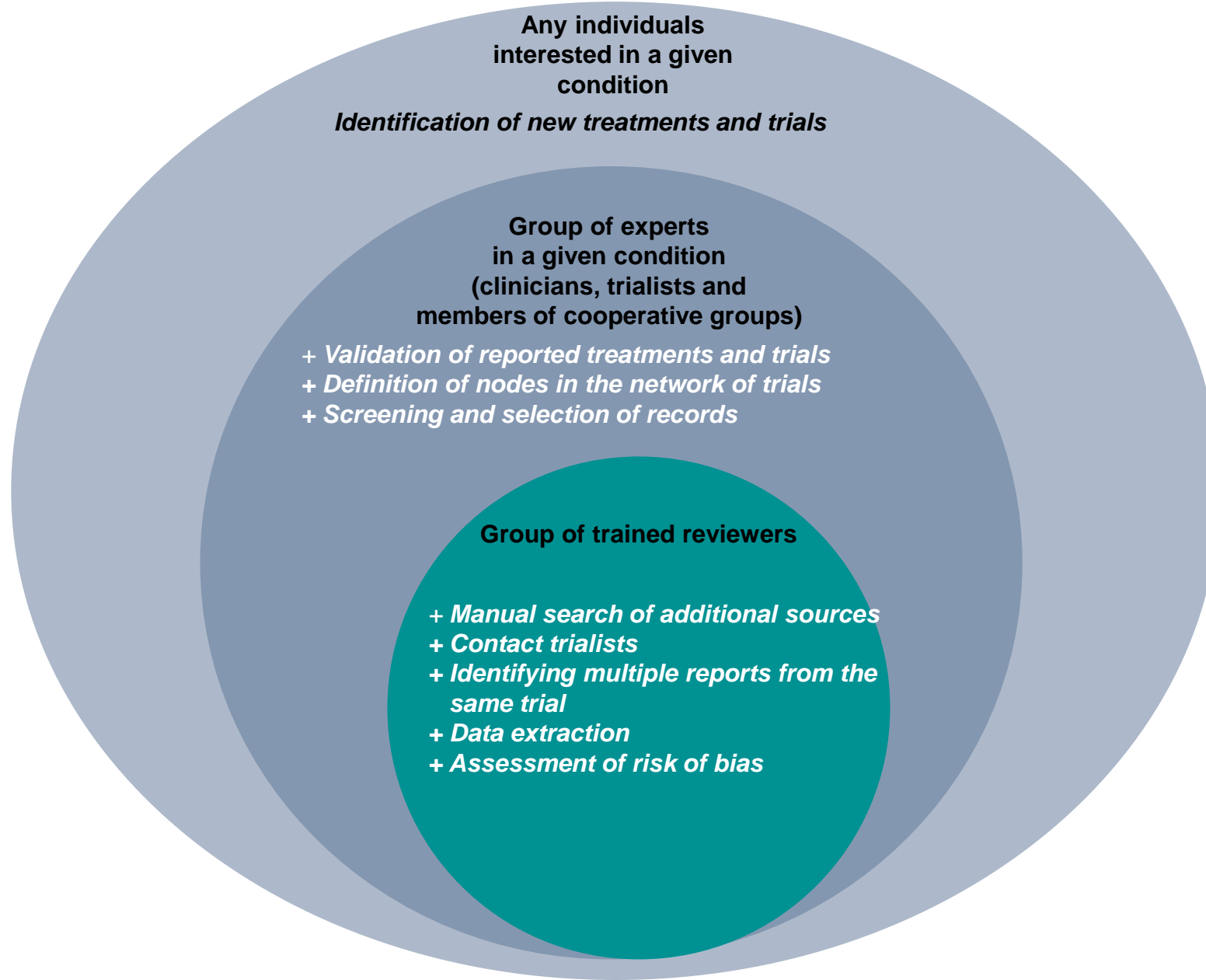
→ Investing a massive amount of resources to produce a NMA and not maintaining it afterwards does not make sense

Pace of evidence generation for 77 network meta-analyses over the last 10 years



Crequit et al, JCE 2019

Moving from a one-shot research investment by **small teams** to a Living NMA maintained by **a community of researchers** for a long period of time



Improving evidence synthesis and beyond

- Developing a **living community for one condition** rather than siloed activities
- A community including systematic reviewers but also clinicians, patients, trialists, methodologists, statisticians and guidelines experts
- Leveraging this community to improve beyond evidence synthesis the whole production of evidence

Living community for one condition rather than siloed activities

Usual tasks of any systematic review
+ additional tasks useful for other purposes

Example of additional tasks:

- Extracting additional data:
eg, for each trial, extraction of the name and address of the PI, the name of his institution, funders
- Assessing of the quality of reporting
- Comparing outcomes used to core outcome set for this disease
- Searching for ongoing trials

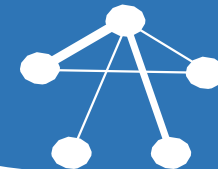
Living evidence synthesis
Living NMA

Living guidelines

Living monitoring of trials
quality and transparency

Living disclosing of the
« quality and
transparency » of trials

Living mapping of research



From living NMA to living guidelines

- Living NMA could help to optimize the guideline development process and to update recommendations as soon as new relevant evidence becomes available
- Improve real-time knowledge transfer by developing living guidelines
- Provide timely, up-to-date and high-quality guidance to target users

(Akl EA et al, J Clin Epi 2017)

From living NMA to Living monitoring of trials quality and transparency

- **Living monitoring of trials conducting quality**
 - Outcomes used vs Core Outcome Set
 - RoB tool Items (High Risk Of B)
 - Avoidable waste (most frequent methodological errors in previous RCTs)
- **Living monitoring of trials transparency**
 - Quality of reporting
 - Protocol access (Y/N)
 - Data-sharing (Y/N)
- **Living disclosing of the « quality and transparency »** of trials by funders, cooperative groups, journals , universities...

From living NMA to Living monitoring of trials quality and transparency

- We can also have a **more proactive and incentive approach to improve transparency**
- We can identify on clinicaltrials.gov and [EUDRACT](http://eudract.europa.eu) all trials as soon as they are terminated and **encourage systematically PIs to**
 - Give access to their protocols,
 - Post their results,
 - Publish their results,
 - Archive their data,
 - Share their data (propose practical repository solutions)

Being proactive for improving transparency

As an example for any trials appearing as terminated trials on CT.gov , we could send :

- Automatic emails to remind PIs and sponsors the law about posting of results (USA and EU) before one year after completion of the trial
- Automatic emails to encourage PIs to plan to archive and share their data and protocol
- Automatic emails if not published after one year

From Living NMA to Living Mapping of Evidence and Gaps in Research

We could help trialists to plan better trials and improve the research agenda by

- Providing an updated mapping of existing and ongoing research
- Helping them to identify gaps to direct future primary trials to the areas for which evidence is most needed
- Providing information about the main methodological limitations of previous trials to avoid doing the same errors

Conclusion

- The evidence synthesis ecosystem needs cataclysmic changes
- Setting up living communities to perform evidence synthesis and beyond could help to improve overall evidence production:
 - more relevant research,
 - better quality research
 - and therefore more useful systematic reviews
- Such pooling will limit duplications and time wasting
- It looks doable with an additional manageable workload

References

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