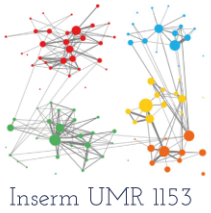

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Towards a New Clinical Research Ecosystem

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The current evidence production system

- Currently, there are 3 distinct production systems contributing to the overall evidence production for therapeutic interventions
  - Primary research (eg Randomised controlled trials or RCTs)
  - Evidence synthesis (SRs and MAs)
  - Guidelines development
- RCTs are considered the ‘gold standard’ by which new medicines, devices, technology, health apps or other interventions are evaluated.

- The highest levels of medical evidence are usually thought to be large RCTs and meta-analyses of high-quality RCTs.

- RCTs and metanalyses are used as the basis for developing treatment guidelines and to inform clinical practice.

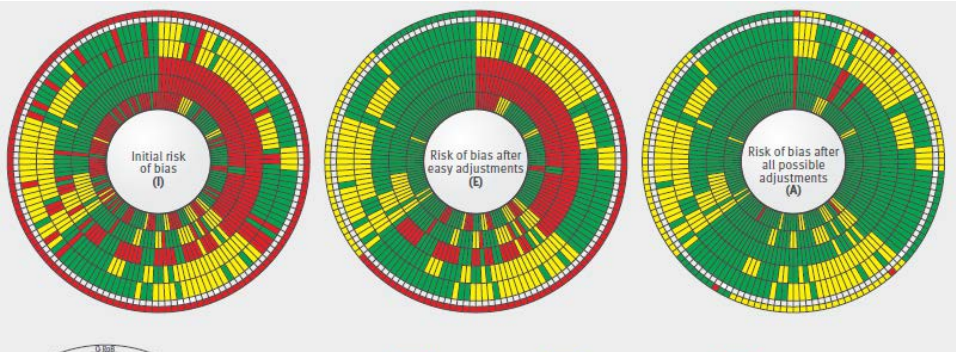
The «evidence» produced is huge

- More than 25,000 RCTs are published each year, and overall more than 650,000 RCTs are available in Pubmed
- The number of systematic reviews and meta-analyses shows a near exponential growth
- Tens of thousands of guidelines and hundreds of thousands of recommendations are developed

However, the current system of production of evidence has been strongly criticized and challenged in recent years ?

Clinical trials are poorly designed and conducted

- Flaws in the design, conduct and analysis are frequent
  - 43% of trials included in Cochrane reviews are at high Risk of Bias
  - Almost half of the pivotal studies forming the basis of EMA approval of new cancer drugs between 2014 and 2016 were judged to be at high risk of bias based on their design, conduct, or analysis
  - Outcomes assessed in RCTs are highly heterogeneous,
    - Critically important Outcomes are not measured or measured differently (eg, 2194 different rating scales in schizophrenia)
- This waste could be partly avoided by simple and inexpensive methodological adjustments .



Yordanov , BMJ 2015
Naci, BMJ 2019
Miyar, Schizophr Bull 2013

Clinical trials are poorly reported

- Half of completed RCTs are never published
- Selective reporting of statistically significant clinical trials and outcomes are frequent
- Important outcomes are frequently missing (eg, only 26% of trials assessing non-opiod analgesics in adults after major surgery reported serious adverse events)

Such reporting bias lead to unrealistic and misleading estimates of drug effectiveness

The generalizability of the evidence from RCTs is challenged

- Missing or incorrect comparators (few head-to-head comparisons)
- Research settings are not typical of community
- Patients are highly selected
- Relevance of outcomes is low (physiologic or surrogate outcomes rather than patient important outcomes)

The failure of the current systematic reviews system

- The current process leads to a series of disparate systematic reviews in terms of selection criteria, search dates, methodological quality, and overlapping scope.
- To address the global picture, making an overview of these multiple systematic reviews is inherently complicated for researchers and not doable for physicians and patients.

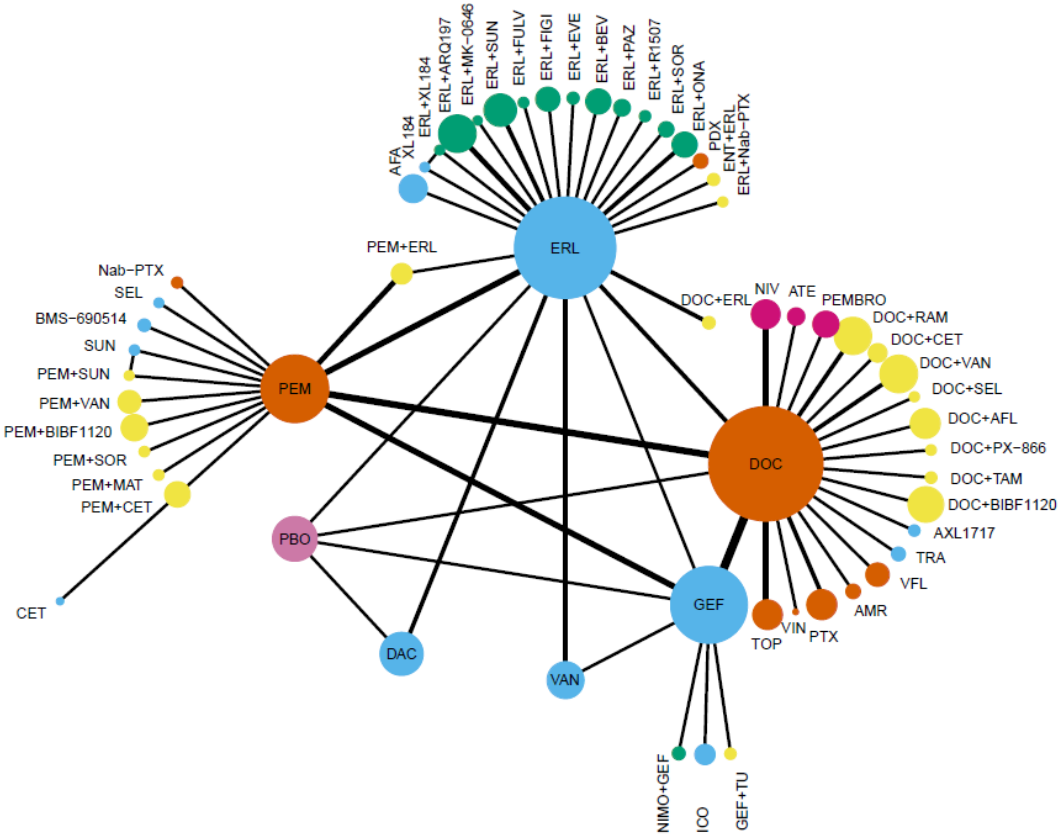
Example of 2nd line treatments of advanced Non-Small-Cell Lung Cancer

Treatments (n=58)

Trials (n =92)

Patients (n=32 434)

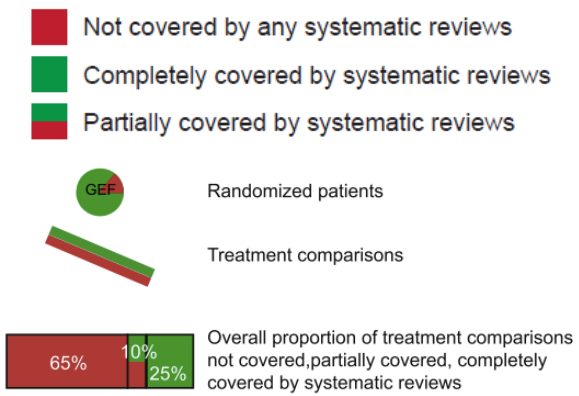
29 Systematic reviews



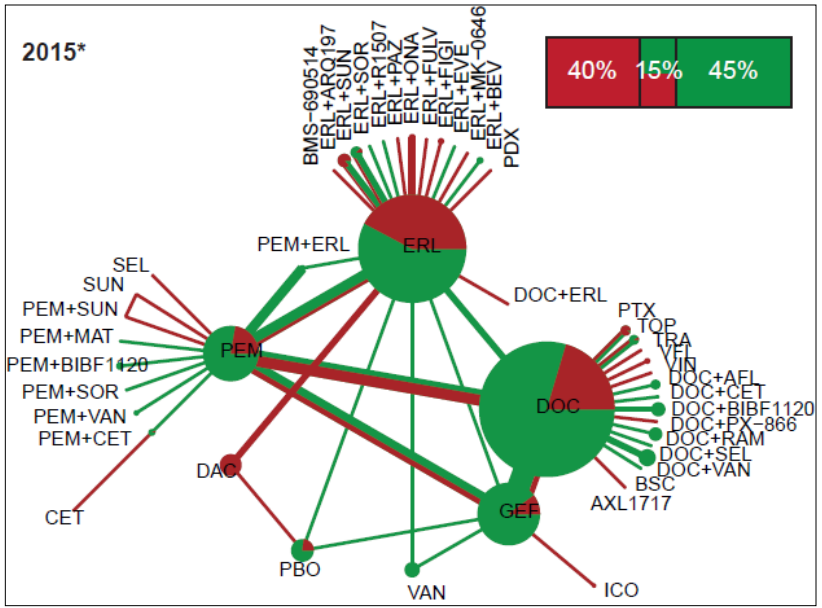
Monochemotherapy
Targeted therapy
Chemotherapy+Targeted therapy
Dual targeted therapy
Placebo
Immunotherapy

Evidence is missing from systematic reviews

- Even when considered collectively, the series of exiting systematic reviews does not provide a complete and up-to-date synthesis of evidence for a given condition.
- For each year from 2009 to 2015, we constructed in the field of lung cancer cumulative networks of randomized evidence.
- Evidence covered by all existing systematic reviews was consistently incomplete with
  - 40% to 66% of treatments missing
  - 45% to 70% of trials missing.
  - 30% to 58% of patients missing



(Crequit, BMC Medicine 2016)



The current systematic reviews do not 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 existing interventions for a given disease which of these interventions works best ?**

- To this end, reviews should ideally incorporate
  1) all treatments available for the condition of interest
  2) all clinical trials assessing these treatments.

Doubts about Meta-analysis of RCTs

According to the Academy Health Report in 2009

- « As much as we all loved randomized effectiveness trials, it is an **unrealistic expectation that we will have randomized trials for every intervention and its combinations in every patient subgroup »**

- « We need Effectiveness evidence in a timely manner. Randomized trials take time to conduct »

- « Therefore, 85% of the CER evidence is from **non-experimental data!*** »

* Academy Health Report June 2009

Individual Patients Data Meta-analyses of RCTs

- Despite their usefulness is evident , such meta-analyses are very rare mainly because having access to all data is extremely difficult
- Initiating IPD meta-analyses in many fields is impossible
- As an example we have shown in orthopaedic surgery that:
  - Among the 38 research questions identified, we could have access only for one question to more than 50% of participants
  - Overall, we were able to obtain data only for 15% of eligible patients

(Villain B , BMC Medicine 2015)

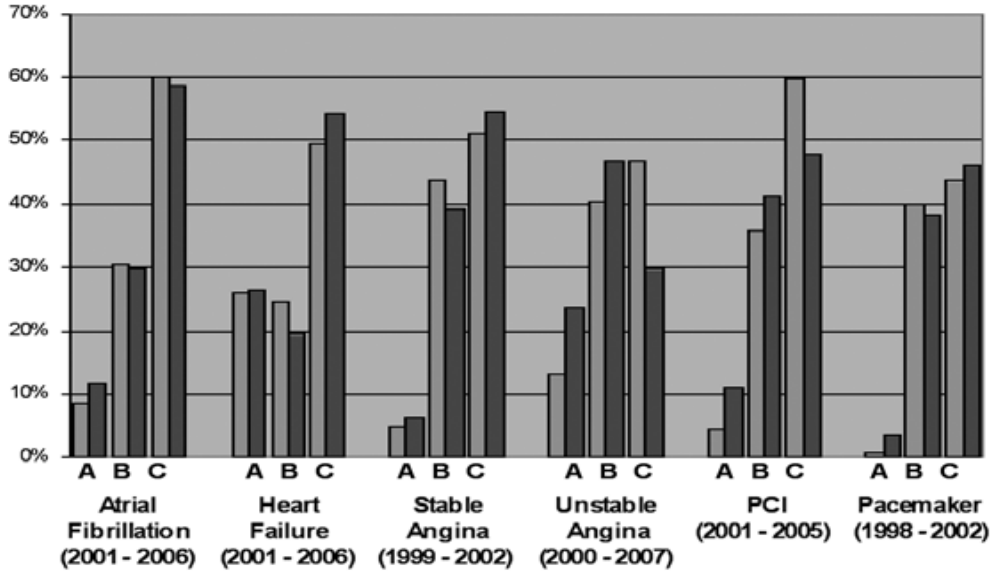
The growing negativity toward meta-analyses

- The meta-analysis are only as good (or as bad) as the studies they include
- If the data are poor, the product of the meta-analysis will be poor as well.
- Controversy : The gravy train of systematic reviews (Richard Horton, The Lancet 2019)

« But what if the astonishing energy, commitment, and productivity of the systematic review community are poisoning rather than nourishing medical practice? »

Guidelines are not based on high level of evidence

- Only a small percentage of recommendations are supported by evidence from multiple RCTs or a single, large RCT
- Among recommendations in major cardiovascular society guidelines such as ACC/AHA guidelines only **8.5% among the 2930 recommendations** from 26 current guidelines are supported by high level of evidence
- In fact, in any current guideline, there are only a handful of very strong recommendations, based on multiple, consistent RCTs level evidence.
- This pattern does not appear to have meaningfully improved from 2008 to 2018 (and previously Tricoci et al did not show improvement from 1984 to 2008).



Tricoci, JAMA 2009 ;
Fanaroff, JAMA 2019;

Break down siloes to accelerate the production of evidence

- **These 3 production systems (trials, systematic reviews, clinical guidelines) largely function in parallel or in silos**
- These systems are **actually highly interdependent** (the quality of guidelines and meta-analysis is dependent of the quality of trials)
- However such interdependency is limited **to data not organisation**
- Reinforcing the link between trialists, systematic reviewers ans guidelines developers is a major objective to implement a virtuous circle of continuous improvement in the quality of evidence
- **It is critical to identify new ways for collaboration between trialists, systematic reviewers and guidelines developers to create space for real changes to occur**

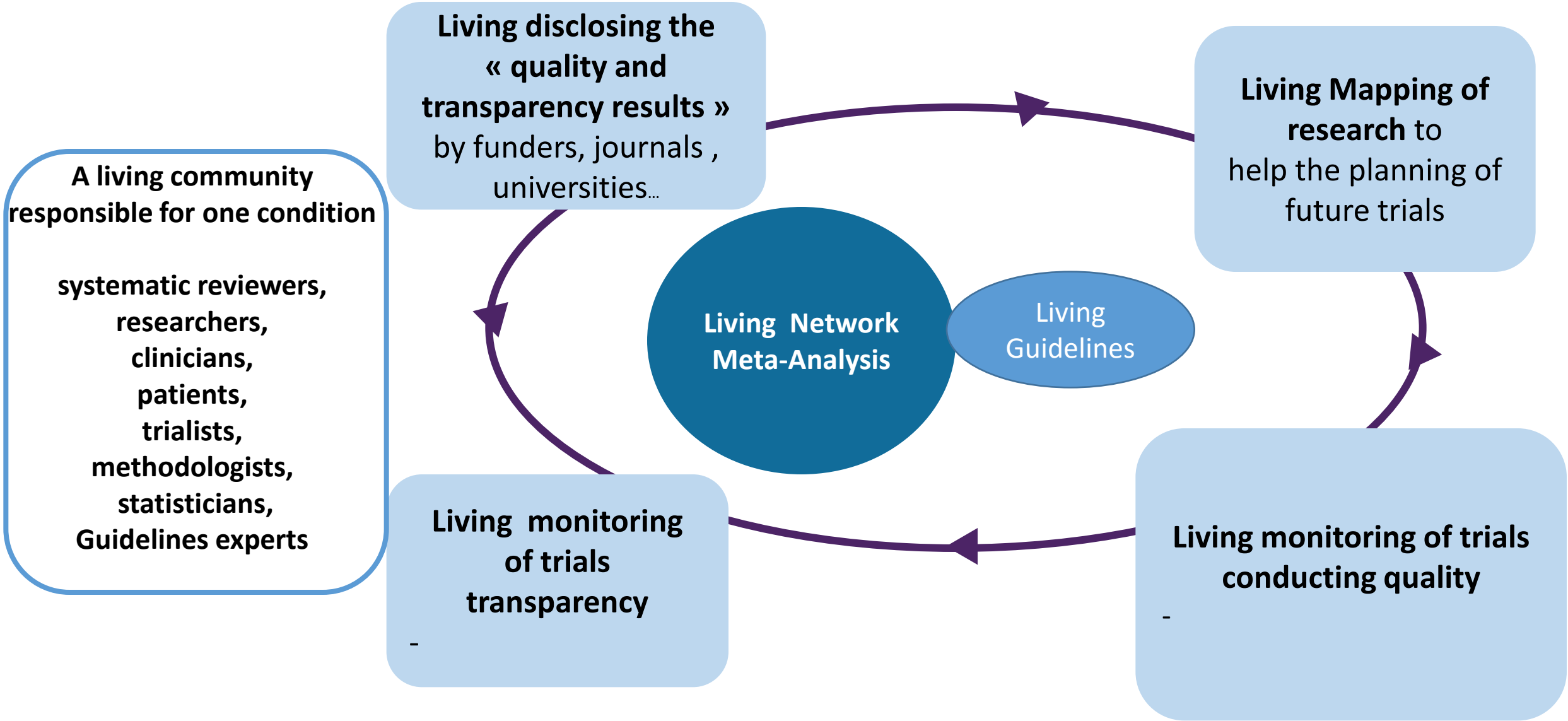
Proposal

- Developing **a living community for one condition** rather than siloed activities)

- Bringing together this community including clinicians, systematic reviewers,patients, trialists, methodologists, statisticians and guidelines experts accepting to join their efforts to improve research and the production of evidence in a field

- Leveraging this community to improve beyond evidence synthesis the whole production of evidence (choice of the research question of interest, quality of the design and reporting of trials, datasharing…)

Developing a culture of continuous improvement of clinical research for a specific disease



Living Mapping of Evidence and Gaps in Research

Such a community 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 in the field to avoid doing again the same errors
- Helping trialists to anticipate further datasharing (providing them counselling about their trial consent forms)

Living monitoring of trials quality and transparency

Such community could organize a

- 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

This community could also organize the living disclosing of the « quality and transparency » of trials by

- funders,
- cooperative groups,
- journals,
- universities…

Living monitoring of trials quality and transparency

- Such a community can also have a **proactive and incentive approach to improve transparency**

- This community can identify on clinicaltrial.gov and EUDRACT all trials as soon as they are terminated and could send emails
  - **To remind PIs and sponsors the law requiring the posting of results** (USA and EU) before one year after completion of the trial (we have evidence that it works, for 10 emails sent there is one additional trial with results posted)
  - **To encourage systematically PIs to**
    - Give access to their protocols,
    - Archive their data,
    - Share their data

(Maruani BMJ 2014)

From a series of meta-analyses to a living network meta-analysis

- I propose switching :
  - From conventional meta-analyses to living meta-analyses
  - From living meta-analyses to a global living network meta-analysis for one specific condition

- In practice :
  - from a series of disparate 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)

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)

Conclusion

- The overall production of evidence system needs dramatic changes
- Bringing together the different communities interested by a particular condition would of mutual benefit for them
- Setting up living communities to improve overall evidence production could be helpful for developing:
  - more relevant research,
  - better quality research
  - and therefore more useful systematic reviews and guidelines
- Developing such community effort may be a game changer to transform their field

Be a
game changer.
Because the world
has enough
followers.

- Absolutely Abbey

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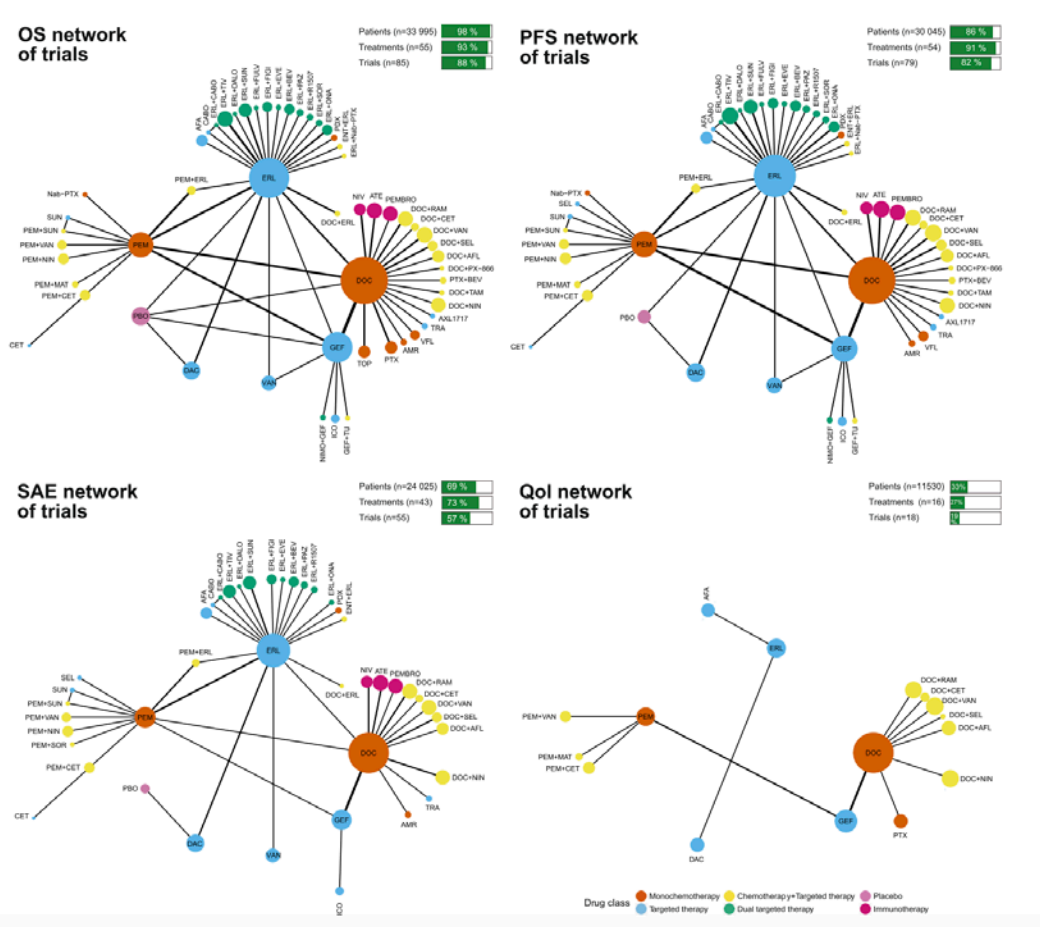
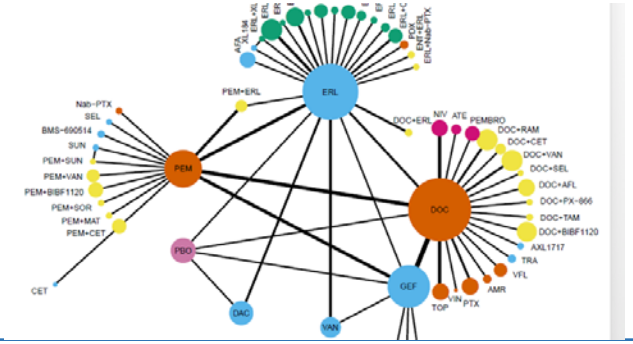
The failure of the current systematic reviews system

- 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


OS network of trials
Patients (n=33 995) 98 %
Treatments (n=55) 93 %
Trials (n=85) 88 %
PFS network of trials
Patients (n=30 045) 86 %
Treatments (n=54) 91 %
Trials (n=79) 82 %
SAE network of trials
Patients (n=24 025) 69 %
Treatments (n=43) 73 %
Trials (n=55) 57 %
QoL network of trials
Patients (n=11530) 33%
Treatments (n=16) 19%
Trials (n=18) 4%
Drug class
Monochemotherapy
Chemotherapy+Targeted therapy
Placebo
Targeted therapy
Dual targeted therapy
Immunotherapy

Reinventing the production of evidence system
Bridging the gap between trialists and meta-analysts

Living network of current evidence and ongoing evidence



Improving evidence synthesis

- Improving access to updated global evidence synthesis (living NMA)
- Improving real-time knowledge transfer (living clinical guidelines)

Increasing the value of existing research

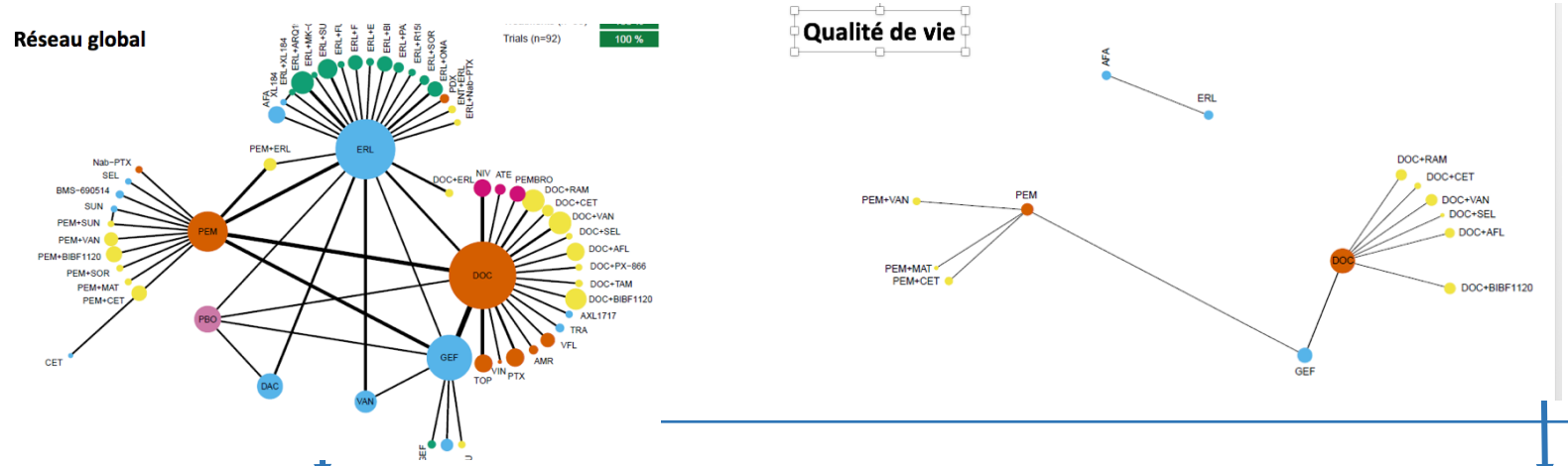
- Increasing
  - Posting
  - Publication
  - Archiving
  - Data sharing
- Avoiding unclear risk of bias (immediate questions to authors)

Decreasing waste in future research

- Providing the networks to help the planning of future trials
- Living monitoring of trials conducting quality
  - Outcomes used vs Core Outcome Set
  - RoB tool Items (High Risk Of B)
  - Avoidable waste (most frequent errors in previous RCTs)
- Living monitoring of trials transparency
  - Quality of reporting
  - Data-sharing (Y/N)
- Disclosing the « quality and transparency results » by funders, journals , universities…

Bridging the gap between trialists and meta-analysts

Live cumulative network of current evidence and ongoing evidence



Terminated trials on CT.gov

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

Published trials

- Immediate evaluation of the quality of reporting and extraction of results and if some points are unclear questions sent to authors
- Automatic emails to ask them to archive their data and to which conditions their data could be shared