Governance of clinical research projects

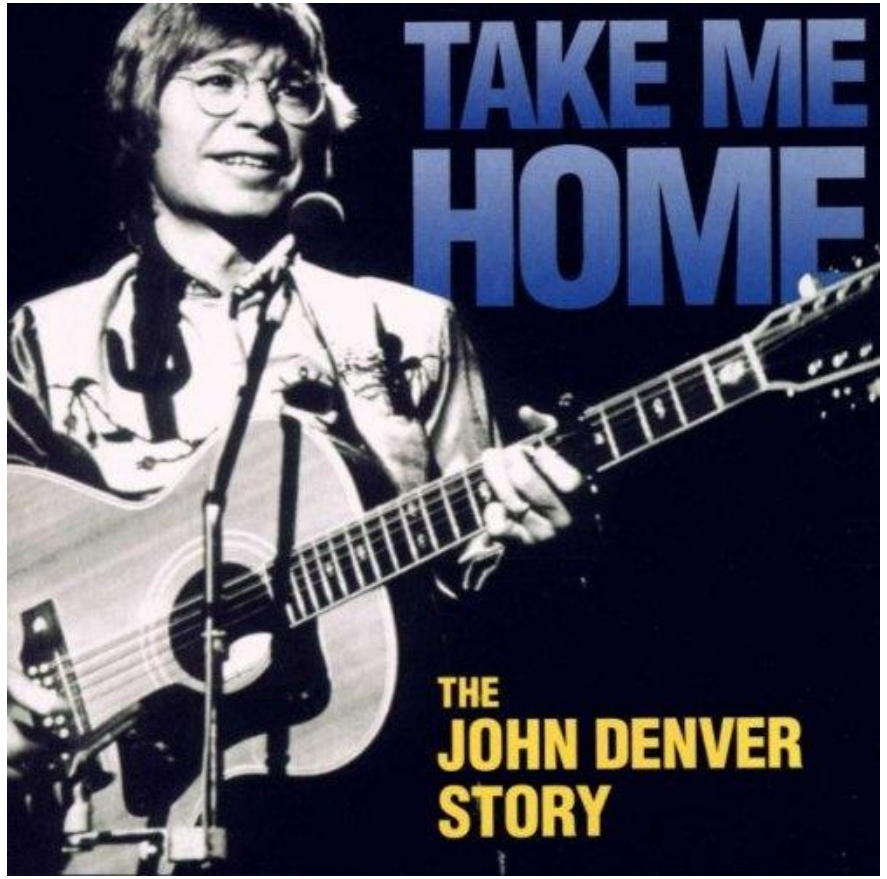
What is it and why do I need to bother?

Sven Trelle, CTU Bern

DCR-CTU Lecture, 26.04.2023

Take home message(s)

- Care about decision-making processes beforehand
- Envisage the possibility for conflicts
- Define governance and decision-making in protocol
- Establish a Trial Management Group (Steering Committee*)
- Think about establishing an Oversight Committee (Advisory Board*)
- Remember, a clinical trial is a long-term endeavor even after publishing it
- * Ensure you define the terms properly in your protocol …

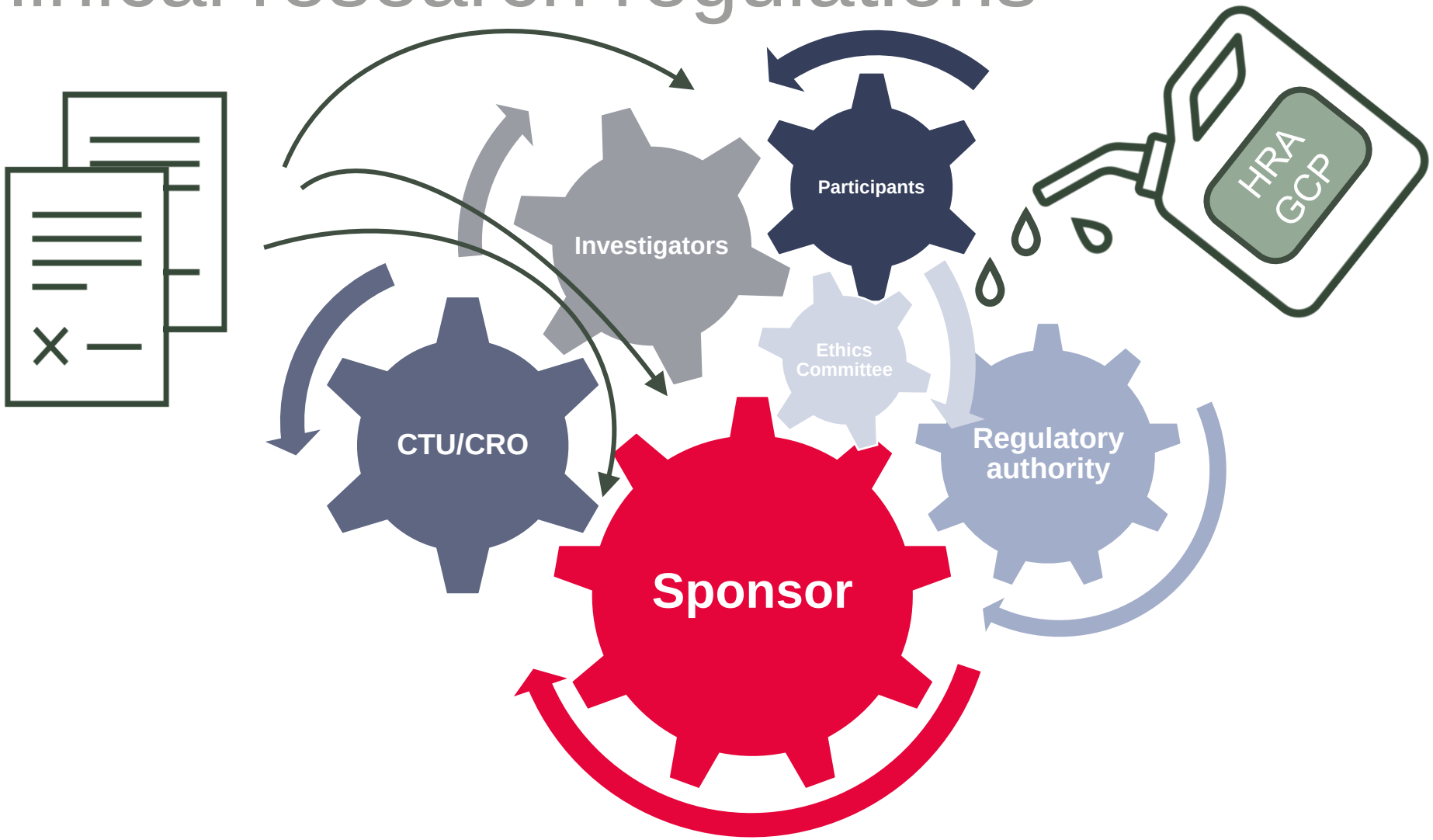


Governance (general)
Some aspects from Wikipedia

- "… the process of making and enforcing **decisions** within an organization or society."
- "… process of **interactions** through the laws, social norms, power (social and political) or language as structured in communication of an organized society **over a social system** …"
- "A variety of **entities** (known generically as governing bodies) can **govern**. The most formal is a government …"

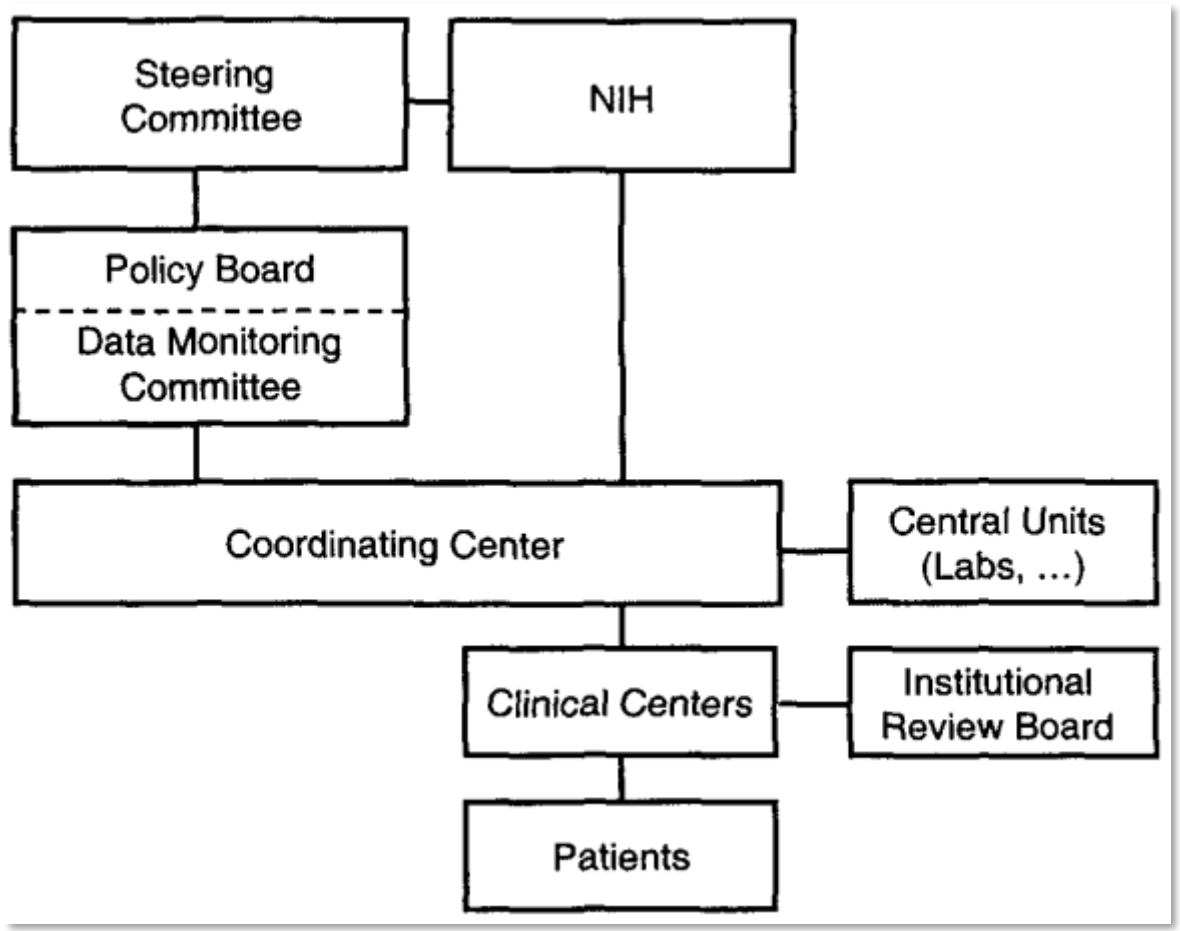
(External) governance

Clinical research regulations



The classical National Institutes of Health model

Some background



Fisher 2001

Policy Board

The classical National Institutes of Health model

- Monitoring of patient safety

→ independent Data Monitoring Committee

→ Previous CTU Lectures

The Steering Committee

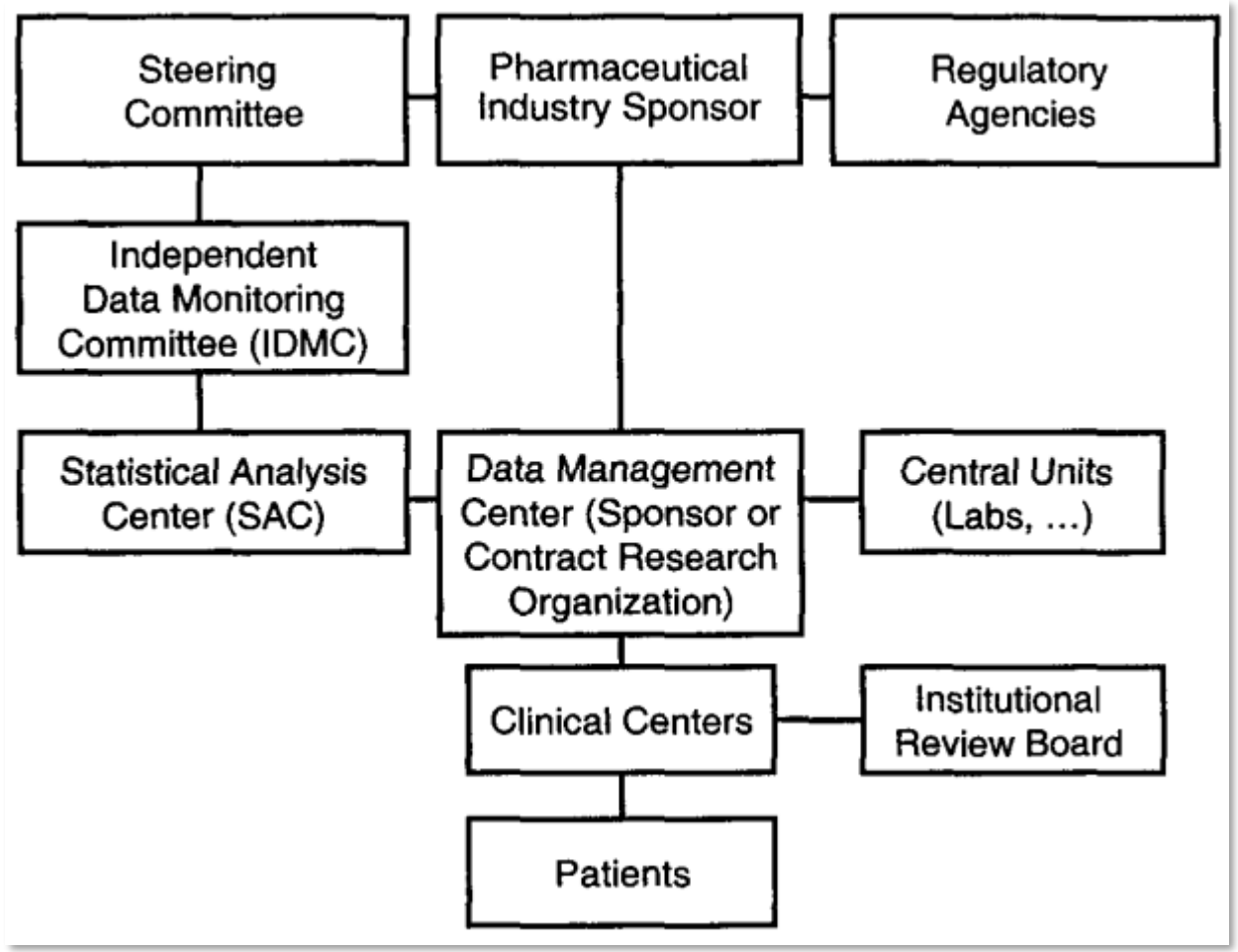
The classical National Institutes of Health model

- Develop protocol
- Intellectual leadership of the trial
- Publish results
- Advice the respective NIH director

- “Study Chair”, representatives of investigators and sponsor (NIH institute)

Modified NIH clinical trial governance model

Industry-sponsored cardiovascular trials

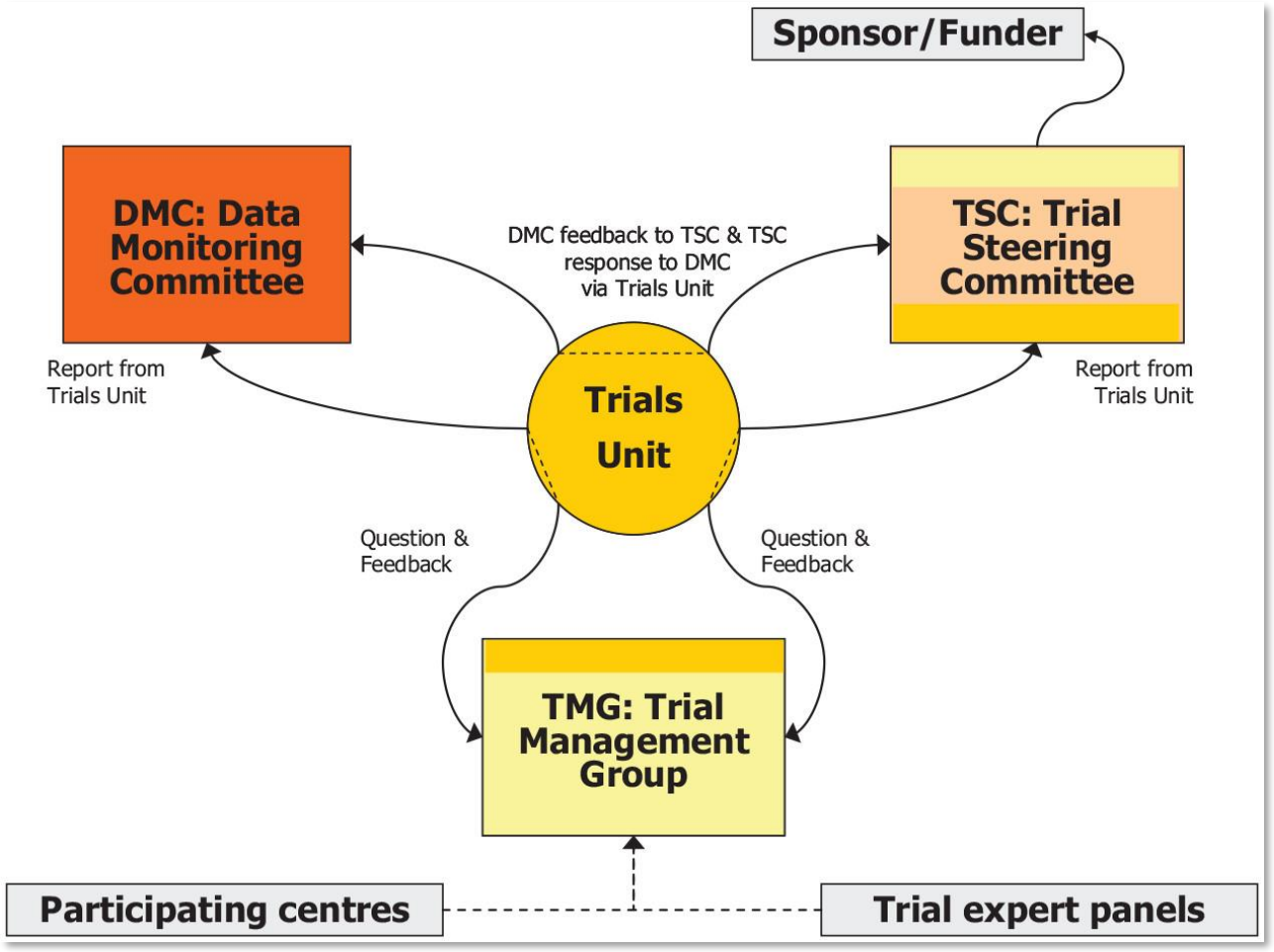


Fisher 2001; DeMets 2002

The UK model (usually)
MRC guidelines for management

- Medical Research Council → funder (not sponsor)
- Chief Investigator → ‘initiator’: responsible for design, conduct, management, analyses, reporting
- Principal Investigator → responsible at trial site
- Sponsor: (usually) host institution of Chief Investigator

Committee structure
UK MRC model



The Trial Management Group
UK MRC model

- To manage the conduct of the trial (day-to-day operations)
- Composition: Chief Investigator (chair), key clinical input, trial operations team (including operations, statistics, programmers), Patient and Public Involvement contributors → not independent

The Trial Steering Committee
UK MRC model

- “All trials should have …”
- To provide independent
  - overall supervision,
  - advise (Trial Management Group), and
  - to ensure conduct according to standards

The Trial Steering Committee
Composition

- Size, membership, meeting frequency → risk proportionate
- >/=50% independent of investigators (including their host institution), their funders, sponsors, etc.
  - Chair → independent
  - >/=2 additional independent members (international if international trial)
  - PPI contributor
  - Chief Investigator
  - 1-2 members of operational team (investigator, statistician, other trial unit staff)
  - As appropriate: ministry/NIH, stakeholder groups (e.g., NGO)
  - Guest: observer from MRC and sponsor

The Trial Steering Committee
Role and meetings

- Patient safety
- Progress
- Protocol adherence
- External new information/data
- Regulatory compliance
- Results dissemination
- Complaints

Empirical data (interviews, ethnography)
Responsibilities

- Advisor (Daykin 2017)

TSC as 'critical friend'	*The ideal function of the Trial Steering Committee [is to] act as a critical friend to the trial, whereby they support the trial to some extent but then they do also ask the awkward questions and hold them to account.* (50, Senior statistician)
	It was really important to have that external objective view of looking at the data independently, but also, them being our critical friends, advising us and supporting us through this... they're there to support and help, they're not just there to chastise. (40, Senior trial manager, trial 7)
TSC as provider of 'tough love'	*[The role of a TSC] is, I think, tough love. (Laughter)... They've got to be on your side... Because if you've got a TSC that's against you, you might just as well hand the money back now. (Laughter)... They've got to kind of be in your corner, but I think they've got to be tough.* (20, TMG member, trial 4)
	If I don't walk out of these meetings feeling like I've been given a bit of a kicking then they haven't done their job properly, that's what they're there to do ... it's their job to... point out the things that we should be doing better. (23, CI, trial 5)
TSC as 'critical advisor'	Interviewer: *When I've asked that question of other people, they value the TSC being a critical friend.*
	42, TSC Chair, trial 8: *No, you can't. It's not a friend. A friend implies that the relationship is a good one and always amicable. I wouldn't hesitate to be a non-friend if I thought it was wrong. Critical adviser – better. However, friend does imply that, "We'll sit round the table like friends and we'll just discuss this and what we say will be okay for you." So criticism; yes, advice; yes. Friendship almost comes as a side issue.*
	Interviewer: *Perhaps the friend bit was them implying that you need to be on their side?*
	42, TSC Chair: *You're not.*
	Interviewer: *You're not?*
	42, TSC Chair: *No. You're independent. So the words of wisdom that you give may be words they don't want to hear. Maybe we're going to say, "Right, this trial needs to be shut. It's not working." That's happened three or four times it the last couple of years, in other trials groups. It's not a matter of cutting your losses. It's a question of making sure that it's the ethically proper thing to do. So I'm very keen that meetings are conducted in a friendly environment but we are there as advisers and critics.*

Some thoughts (my (!) recommendations)

- No generally agreed approach to oversight
- Take a risk proportionate approach but be **explicit** in **protocol** about governance
- Trial Management Group → supervise trial conduct
- Advisory Board* → external advisors (incl. PPI contributor(s)) + internal members
  - Separate Patient Advisory Board
- Data Monitoring Committee → comparative data (interim analyses)
- Sponsor has final responsibility (‘delegated to’/implemented via the Coordinating/Chief/Principal Investigator)
- Umbrella (DMC, SC, TMG) meeting before trial starts
- Think about data access/sharing after end of project

* Steering Committee (UK), PICTO (Partly-Independent Committee for Trial Oversight) or SITOC (Semi-Independent Trial Oversight Committee) (Lane 2020)

Questions?
Thank you for your attention!

References

- Daykin A et al. 2016. What are the roles …, Trials; 17: 307
- Daykin A et al. 2017. 'We all want to …'. Trials; 18: 612.
- DeMets DL, Califf RM. 2002. Lessons learned … Circulation; 106: 880-6.
- Fisher MR et al. 2001. The role of … Drug Inf J; 35: 115-29.
- **Harman NL et al. 2015. Exploring the role … Trials; 16: 597.**
- **Lane JA et al. 2020. A third trial committee … Clin Trials; 17: 106-12.**
- Medical Research Council. MRC guidelines fo rmanagement …. Mar 8, 2022. Available at: https://www.ukri.org/publications/management-of-global-health-trials-mrc-guidelines/. Accesses April 22, 2023.
- Medical Research Council. MRC Short Guide: Trial Steering Committees (TSCs). Feb 02, 2022. Available at: https://www.ukri.org/wp-content/uploads/2022/03/MRC-170322-ShortGuideTrialSteeringCommittees.pdf. Accessed April 23, 2023.
- Wikipedia contributors. Governance. Wikipedia, The Free Encyclopedia. April 6, 2023, 03:39 UTC. Available at: https://en.wikipedia.org/w/index.php?title=Governance&oldid=1148434755. Accessed April 24, 2023.