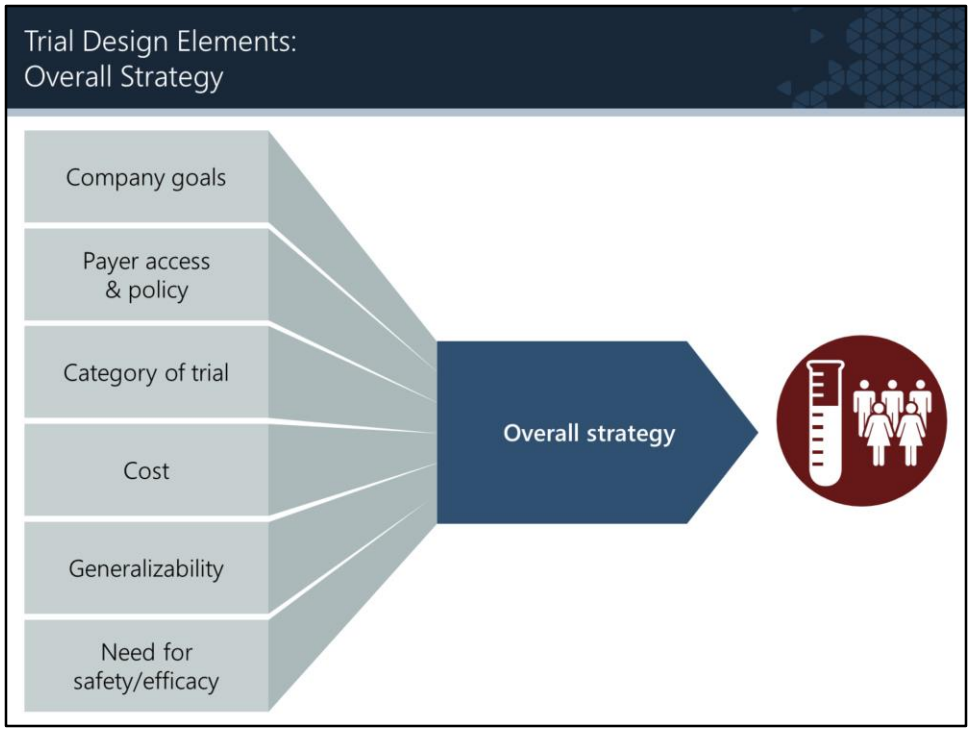
GETTING STUDIES RIGHT TO SUPPORT DRUGS, DEVICES, AND BIOLOGICAL PRODUCTS IN HEALTHCARE

Strategic Solutions, Inc.
Clinical Research Services

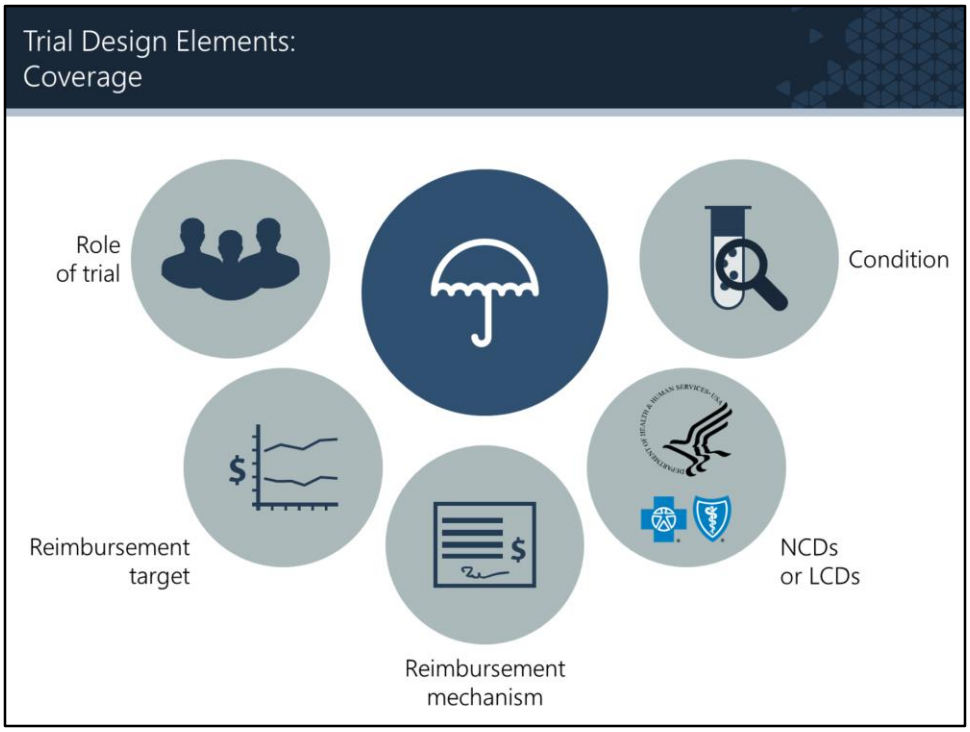
Marissa J. Carter, PhD, MA, MAPWCA
Strategic Solutions, Inc., Cody WY, USA

CLINICAL TRIALS



0- Company goals, payer access and policy considerations (coverage), category of trial, cost, and generalizability to populations versus the need to demonstrate safety/efficacy under controlled conditions *(Inclusion and exclusion criteria, dosage/frequency of application, Regulatory, Safety)* all feed into the overall strategy for trial design.

0- List the goals
1- Rank them
2- Look at the trade-offs, look at cost, and re-rank
3- All stakeholders within the company have a say
4- Form a temporary team if it will facilitate discussion
5- The role of consultants
6- The Real World
7- By paying attention to these aspects you can help to achieve your company's goals.



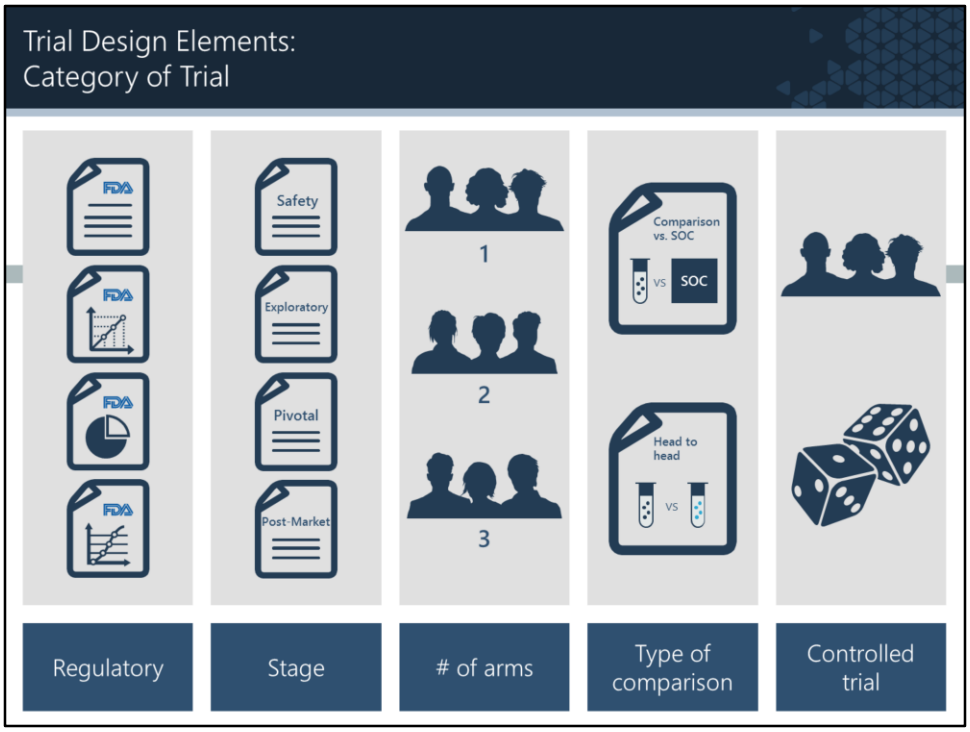
0-What is the role of the trial in getting coverage (key, support, etc.)

1- Reimbursement target (and what the product costs versus what you can essentially sell it for)

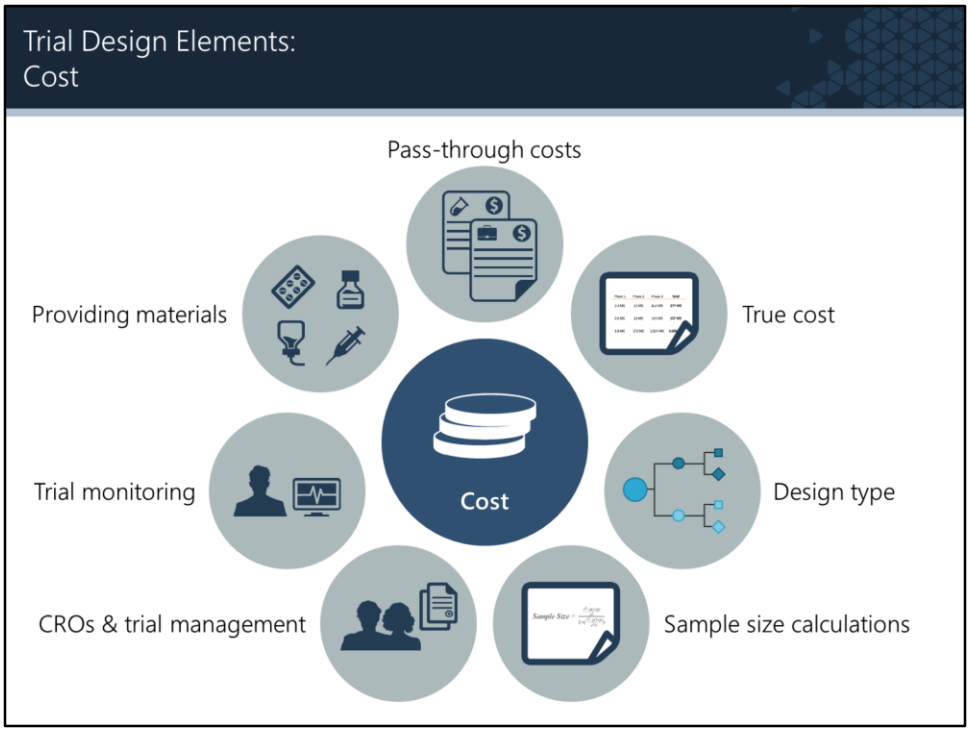
2- How will the drug or product get reimbursed (mechanism)?

3- Coverage via NCDs or LCDs?

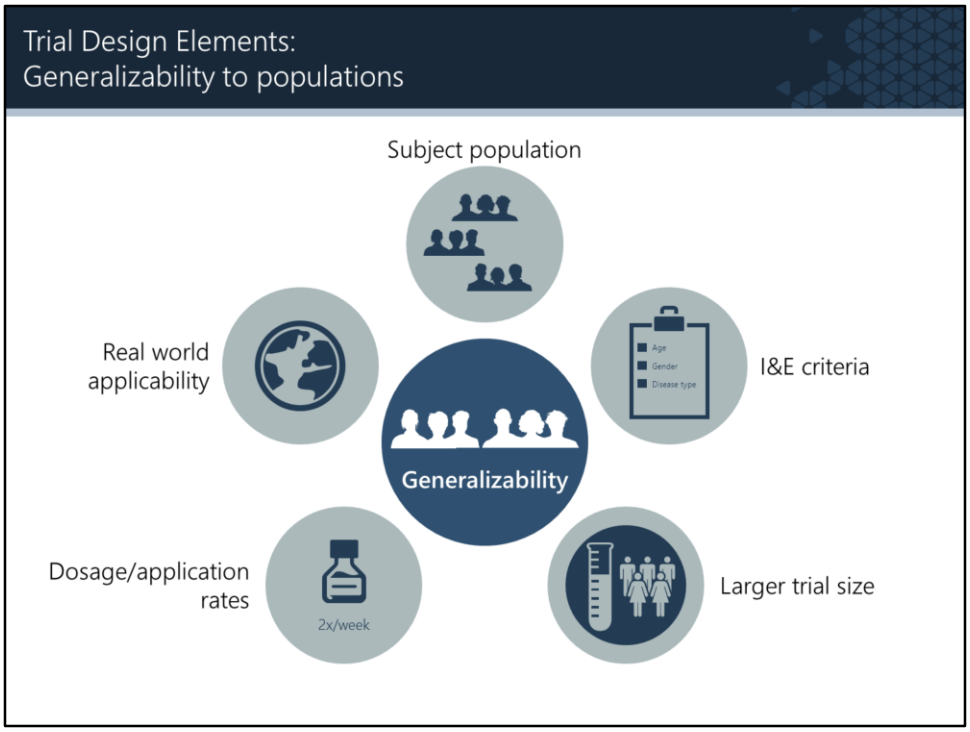
4- What condition(s) are you targeting? Can you use this trial basis for other conditions?



0- Regulatory: approval route/phase
1- Safety, exploratory, pivotal, or post-market?
2- Multi-arm?
3- Comparison versus standard of care or head to head?
4- Controlled trial?



0- Pass through expenses
1- Providing materials
2- Trial monitoring: who should do it?
3- CROs and trial management: one size fits all or specialized?
4- Sample size calculations: how important are they?
5- Design type impacts cost
6- True cost: external trial budgets and internal costs



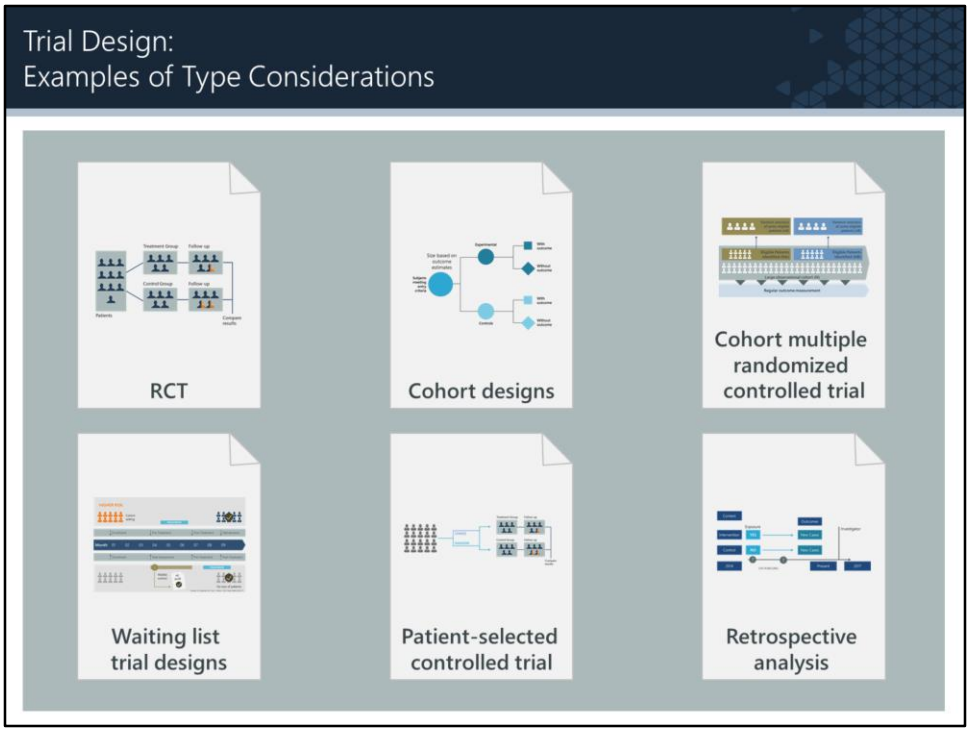
0- Choose your subject population with care

1- Real world is very different from controlled trial world

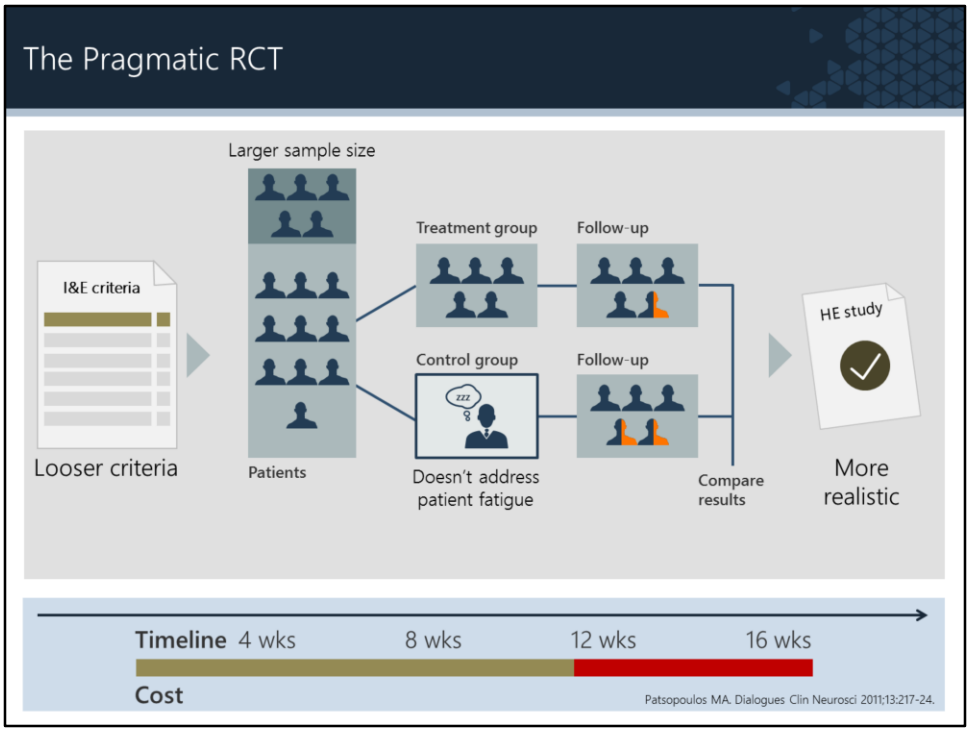
2- Dosage/application rates need to be determined carefully

3- More generalizable trials need to be larger unless your drug/product has amazing efficacy

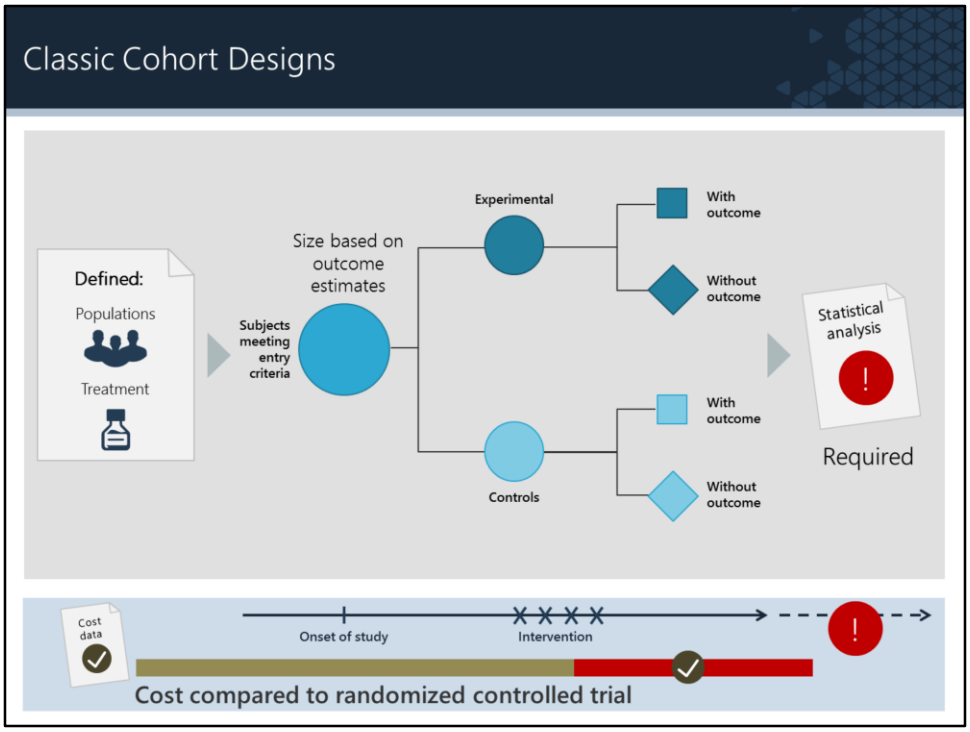
4- I&E criteria will generally be incorporated into NCDs and LCDs until you conduct a broader trial (For regulatory trials this is a key issue)



0- RCTs (e.g., tight, pragmatic, staggered start)
1- Cohort designs
2- Cohort multiple randomized controlled trial
3- Waiting list trial designs
4- Patient-selected controlled trial
5- Retrospective analyses from registries or large healthcare databases



0- Pragmatic RCTs are designed to more mimic real world life and practice while retaining controlled trial characteristics
Typically inclusion and exclusion criteria are much wider or looser ("opening the goalposts")
1- Sample size has to be much larger than usual
2- Health economic analyses may be more realistic
3- Doesn't address patient/trial fatigue for control group(s) unless crossover permitted
4- May be very costly if study period is >12 weeks



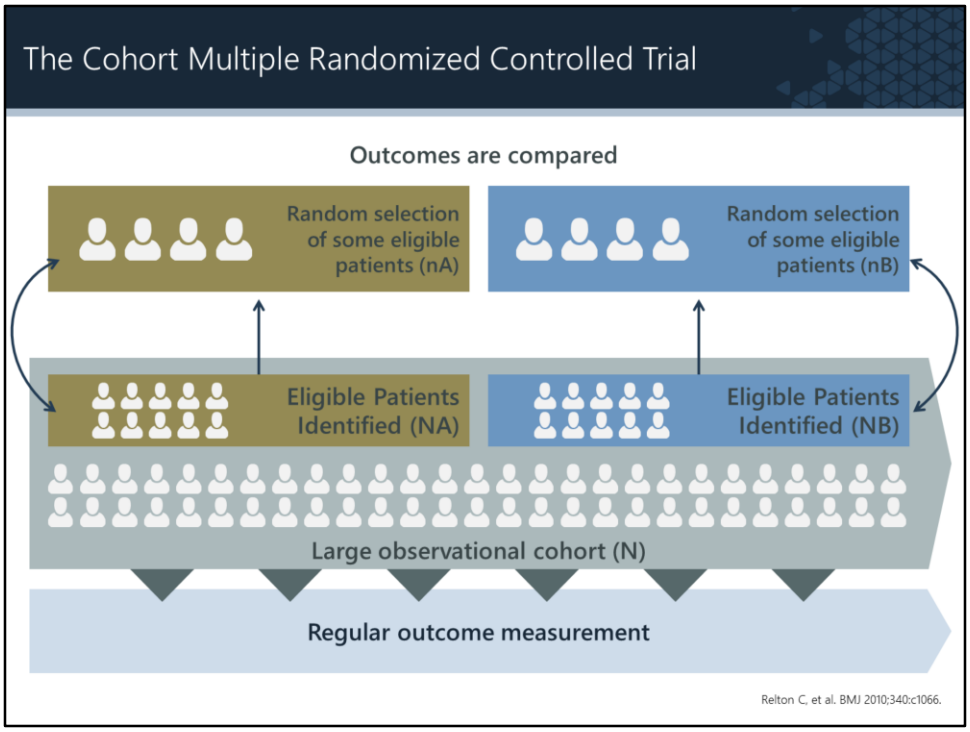
0- Classic cohort designs are much cheaper than RCT and you can collect cost data concurrently

1- Can define populations to be observed, as well as treatments

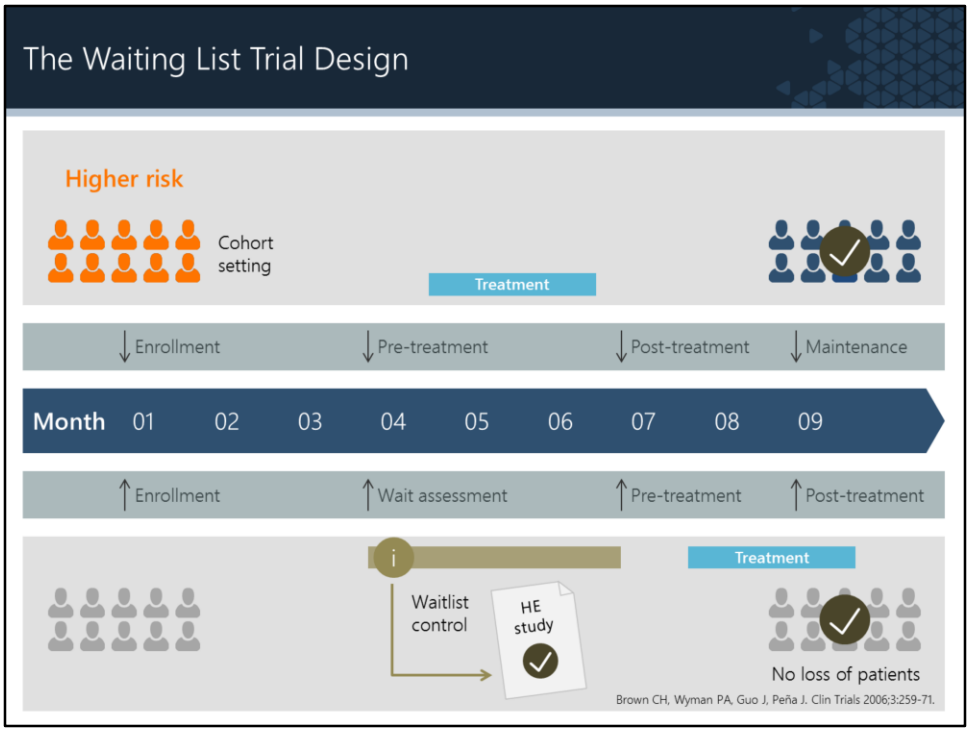
2- Sample size has to be based on reasonable outcome estimates and statistical power

3- Much longer study times can be used, **BUT** may start to lose large numbers of patients.

4- The classic cohort design also requires sophisticated statistical analysis



0- Large observational cohort of patients with problem is recruited (N) and outcomes are regularly measured.
1- For each RCT identify all eligible patients from cohort (NA).
2- Some eligible patients (nA) are randomly selected and offered intervention.
The outcomes of the randomly selected patients (nA) are compared with (NA).
Process can be repeated for further RCTs (e.g., (nB)/(NB)

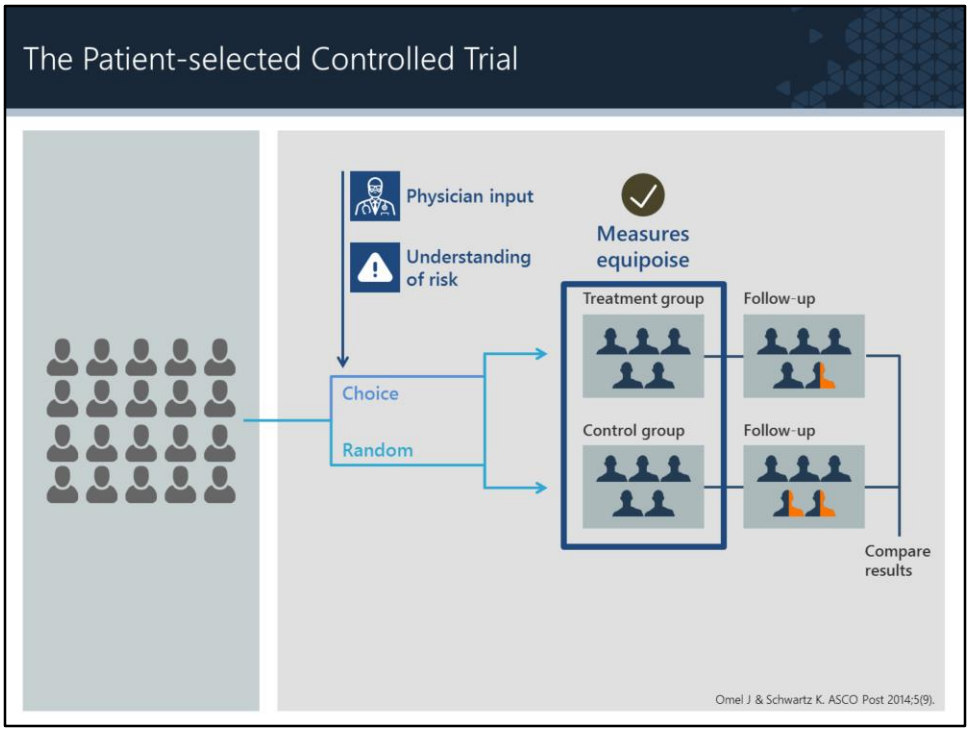


0- A variant called dynamic wait listing permits random assignment to intervention condition multiple times in a trial (alternative to cluster randomization). Randomly assign the same intervention now or later

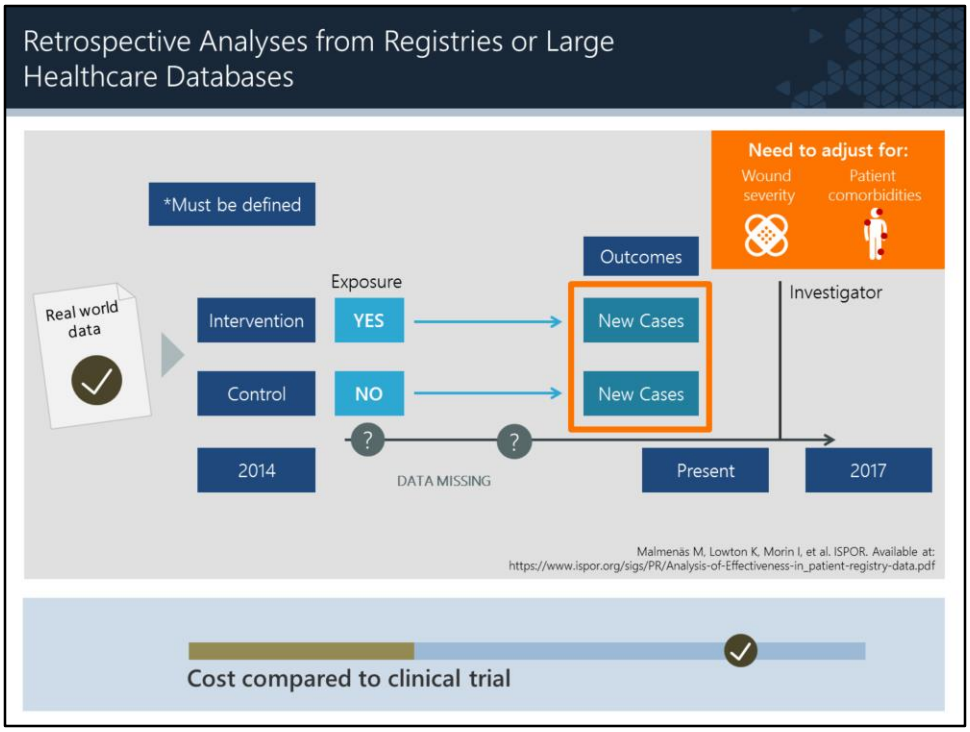
1- Health economic analysis looks at delay; important because in most RCTs the intervention arm(s) has no delay

2- Solves problem of losing patients in trial because the feel they are “not getting the good stuff”

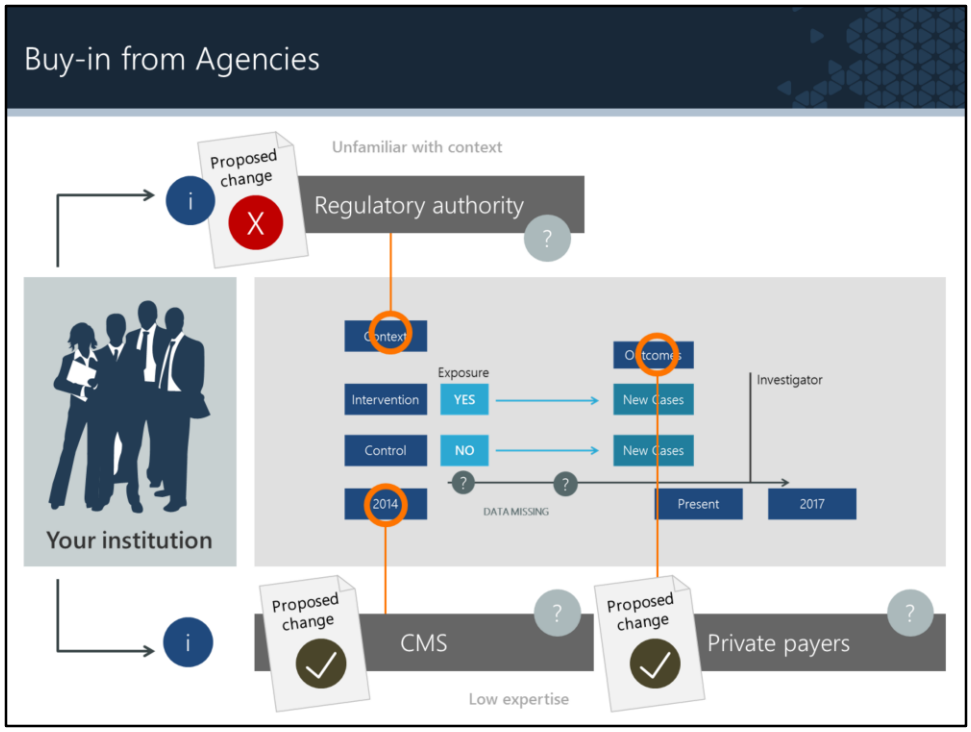
3- Could also use a cohort setting in which a case finding determines allocation (e.g., higher risk of amputation)



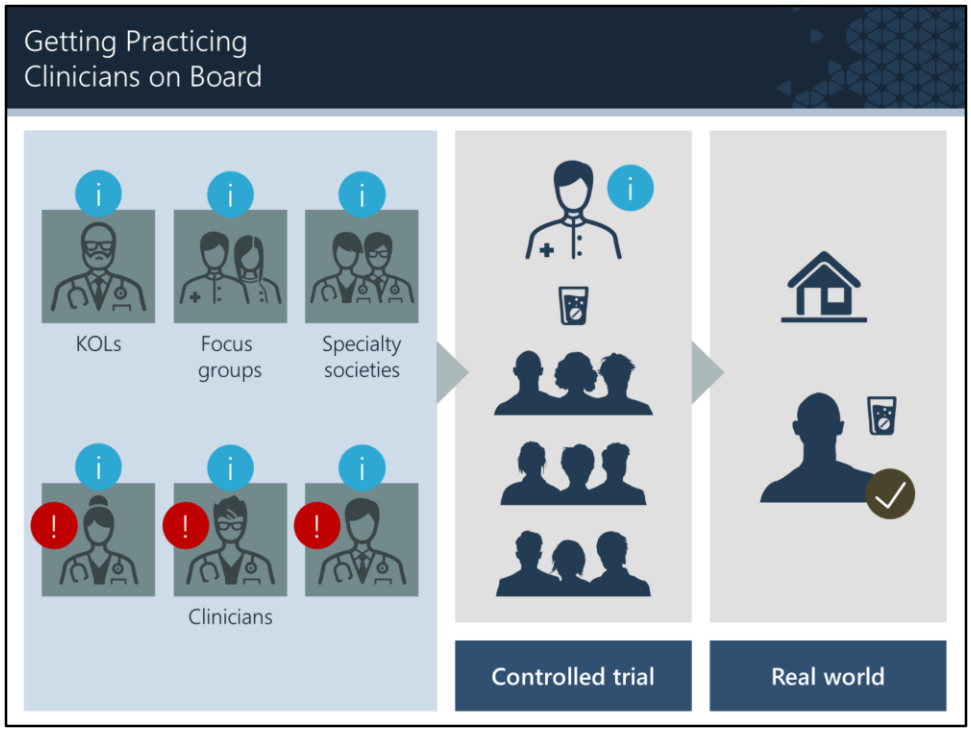
0- New proposal designed to address enrolment/patient retaining issues.
1- Patients would either be happy with random allocation (interventions/SOC) or select the arm they most want to be in based on their understanding of risk and with physician input
2- Distribution to the study arms objectively measures equipoise.



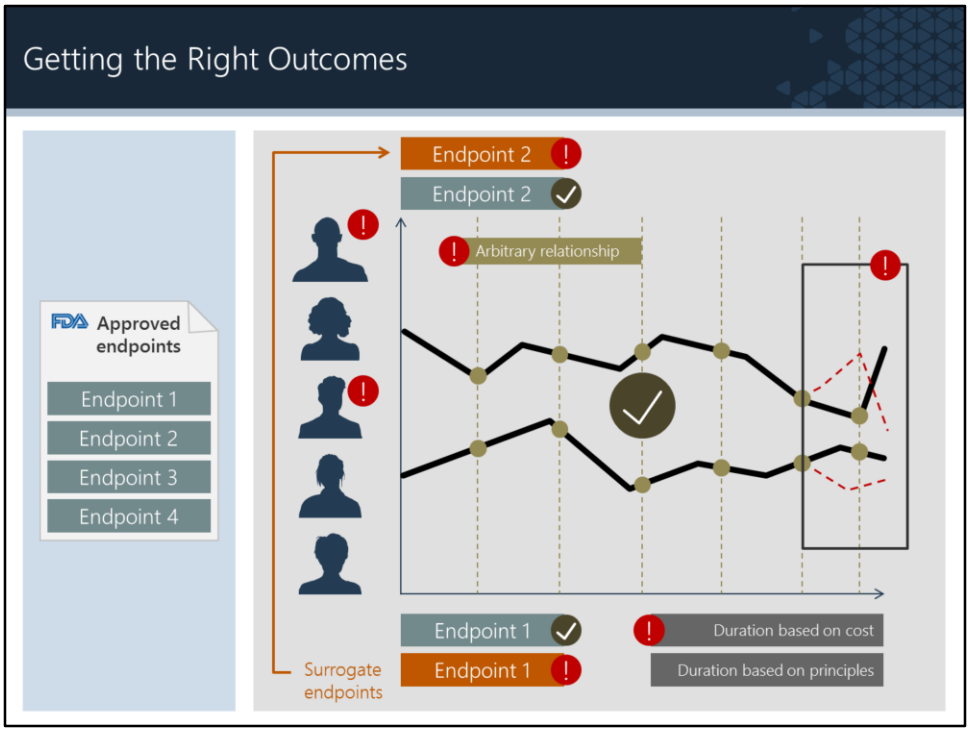
0- Retrospective analyses are relatively cheap to conduct compared to clinical trial
1- You need to define: Intervention/control populations and outcomes and study time period
2- Need to adjust outcomes for wound severity and patient comorbidities; **challenging!**
3- Uses real world data. Missing data may be a big problem



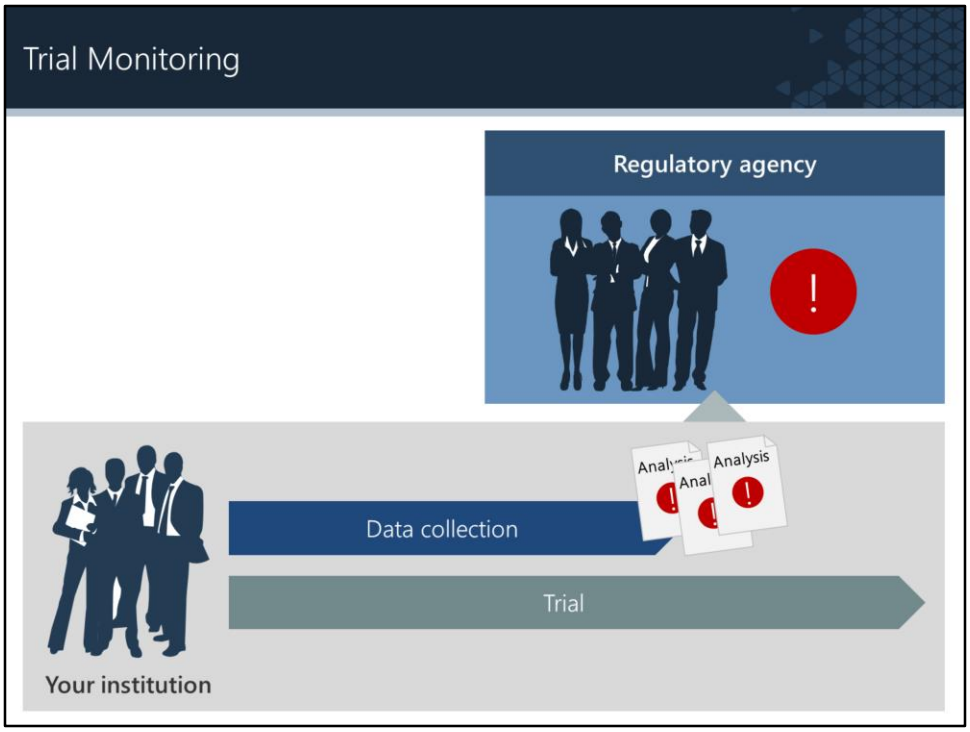
0- Validating design with CMS/private payers. Some may lack serious expertise in EBM and trial design.
Education always worthwhile in the context of reimbursement, but…you may end up with design changes you don't like
1- Regulatory authorities generally know more than you do about trial design but not always the context
2- In any interaction decide what you can live with and what you can't and make your stand.



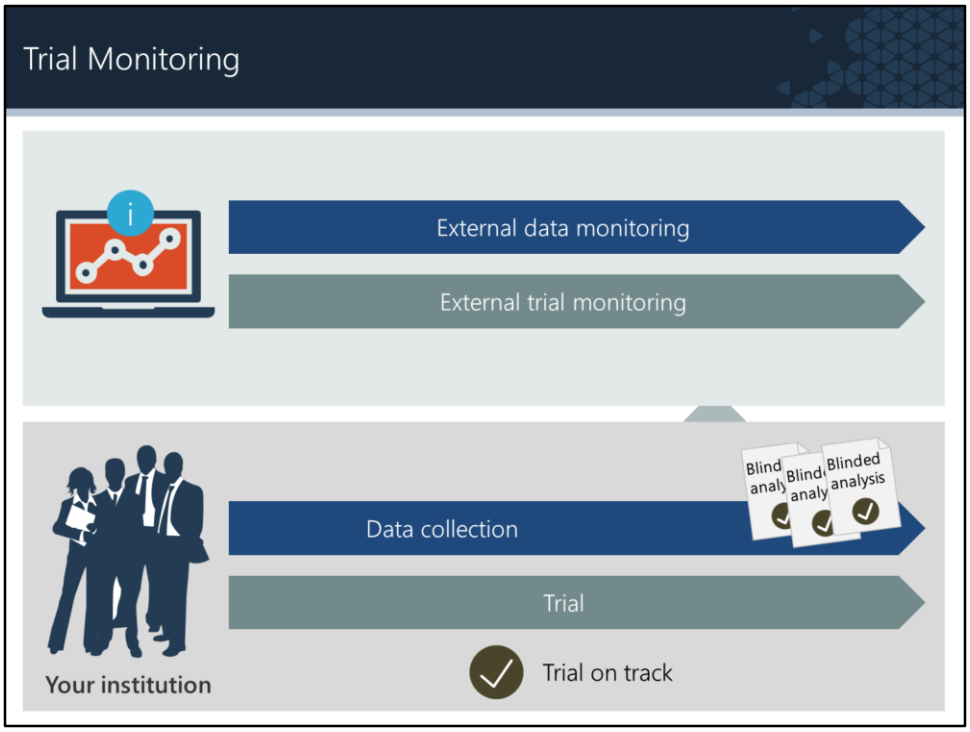
0- Make sure you understand clinician's concerns about the drug/device/biologic
1- KOLs don't know all the answers. You can use interviews and focus groups, specialty societies to get clinicians on board.
2- The controlled world is vastly different from the real world, so you need to make sure results are useful for real world application



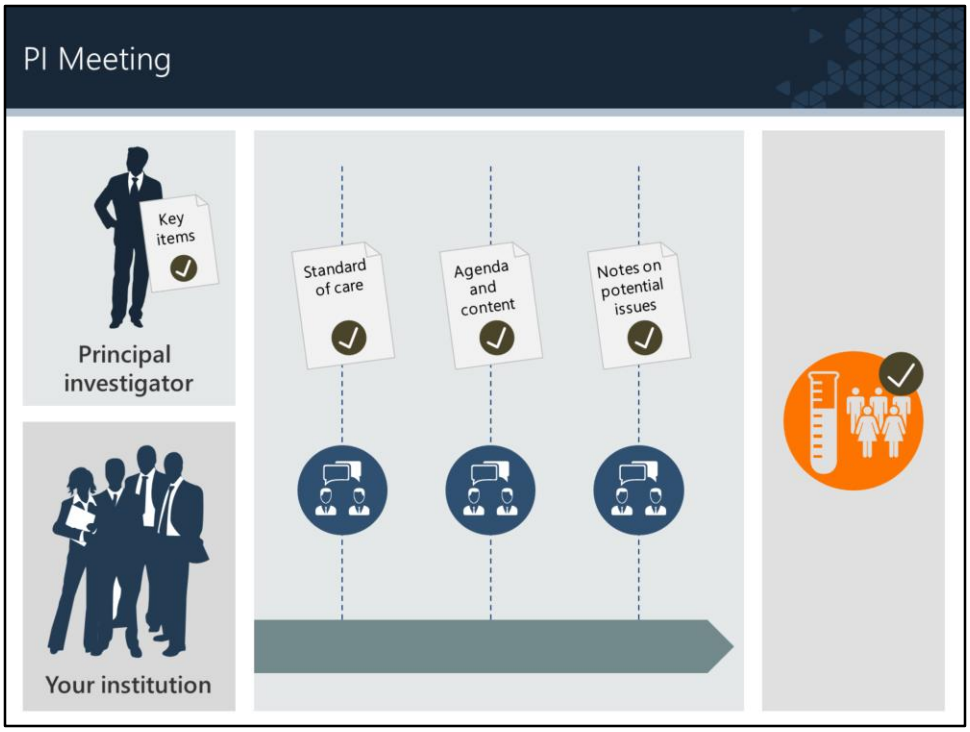
0-Be cautious about surrogate endpoints and study duration based on cost
1- Be especially cautious about composite and arbitrary proportion and time to event endpoints
2- Deliberate exiting of subjects for certain conditions during the trial will affect endpoints sometimes dramatically and to the detriment of the trial
3- Where there are approved FDA endpoints use them
4- Duration should be based on both scientific principles and efficacy/safety considerations
5- This will ensure you are getting the right outcomes



0- Regulatory agencies don’t generally like interim efficacy analyses especially when unblinded (safety ok)

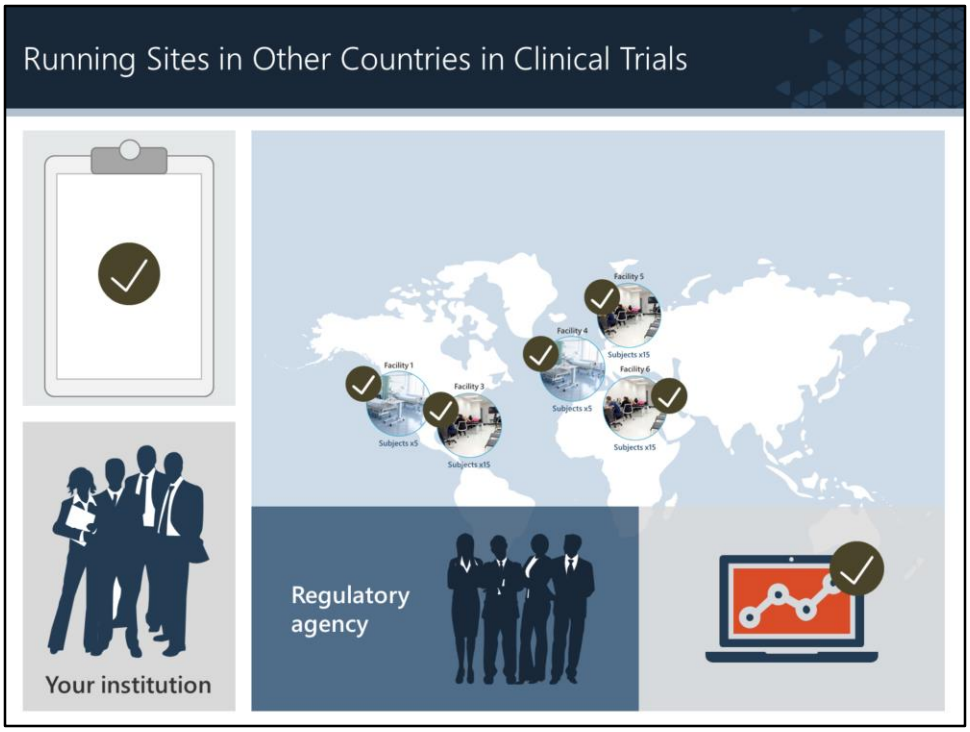


0- Blinded analyses will tell you whether things are on track or not
1- External trial monitoring is critical especially when a single CRO or management organization is conducting the trial. Monitoring of data is as important as site visits.

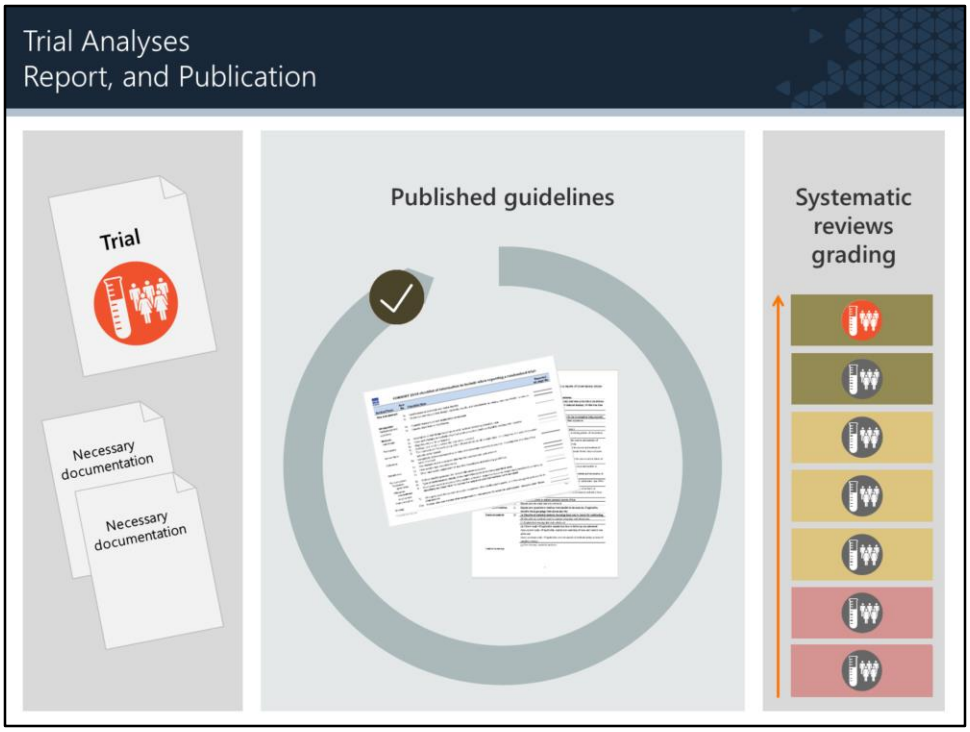


0- The PI sets the tone for everything in the trial. Even experienced investigators need to be reminded of key items
1- Besides the protocol, important to thoroughly review standard of care in context of the study. The agenda and content of PI meetings are critical, and representatives of sponsors should attend and make notes on any deficiencies, potential issues with investigators
2- This is critical for the success of the trial

0- How many sites should a trial have?
1- Initial site visits are important to determine whether the site is fit to enroll subjects. (The need for adequate site infrastructure and personnel)
2- Number of subjects enrolled at each site
3- Recruitment problems can result from the trial design but also individual sites
4- Early external site monitoring tells you whether a site is performing as expected



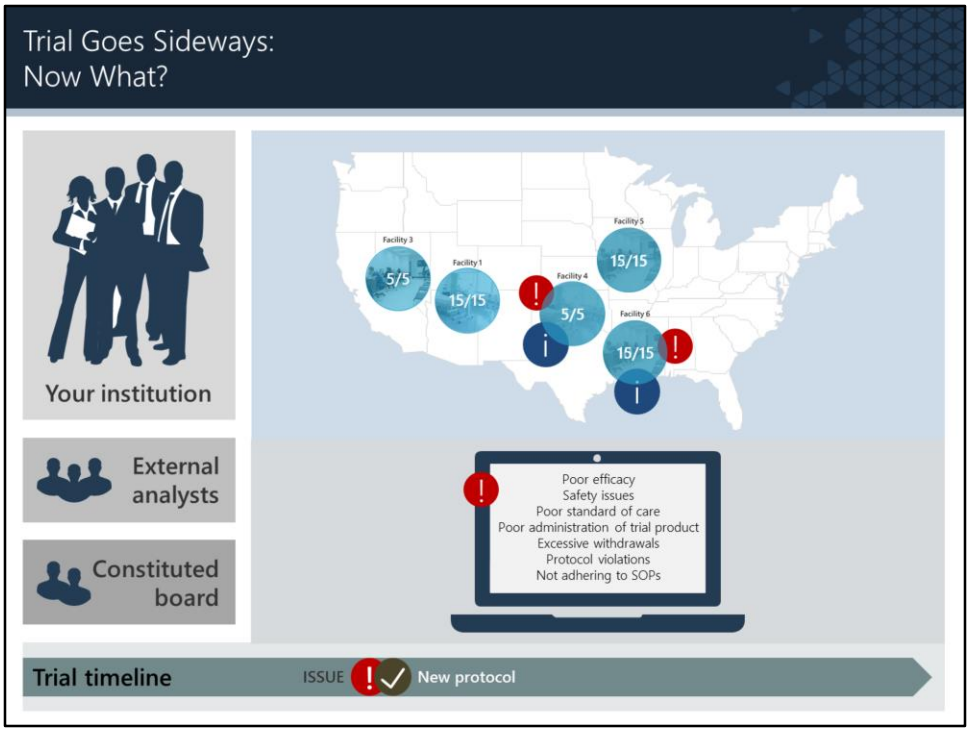
0- The main problems with sites in other countries:
Extra cost (but depends on whether the site is in a developed country)
PI meetings
Standards of care
Site and data monitoring
Language issues
1- The decision to run trials wholly within other regions of the world should depend on demands or requirements with other regulatory agencies and specific advantages of sites in those countries
2- This way you can ensure better outcomes



0- Trial analysis follows the statistical analysis plan. Follow the published guidelines for trial design types (CONSORT, STROBE, etc.); failure to do so may result in the trial being downgraded in systematic reviews.

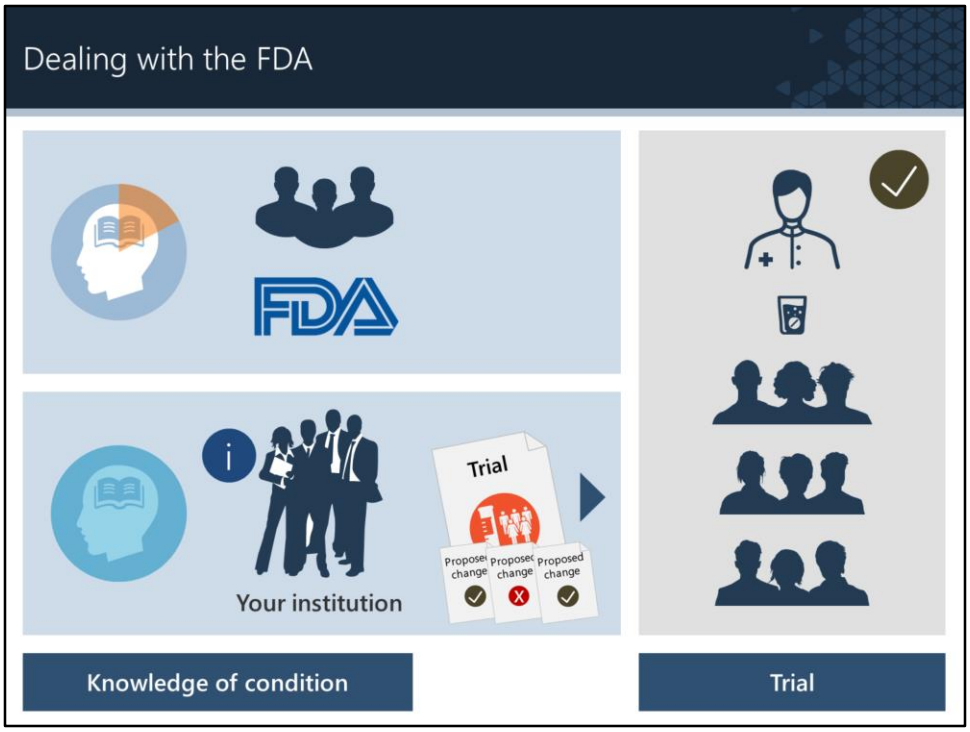
Ad hoc analysis should generally be discouraged unless the trial is exploratory

1- Documentation in the trial report should be sufficient to cover all aspects required in publication. By doing so and following the guidelines, the trial won't be downgraded in systematic reviews.



0- If the trial has an issue,
1- Halt all subject recruitment
2- Determine root causes of trial failure, enlisting constituted Boards or external analysts if necessary. Often the problems can be traced to a few sites
3- Most trials fail due to poor efficacy, safety issues, poor standard of care or administration of the trial product, excessive withdrawals or protocol violations or not adhering to SOPs
4- Decide whether to stop the trial or restart with additional training and/or a new protocol version

0- Most people see the FDA as an adversary but it depends on the division you're dealing with and the group. The FDA generally knows more than anyone else on the best ways to conduct clinical trials, however, they may not understand the condition you are trying to treat in the same way you do
1- Look at proposed changes in terms of scientific credibility and cost impact



0- Pick your battles carefully based on the above.
1- with this approach you will be able to conduct better trials

ANY QUESTIONS?

Email us at info@strategic-solutions-inc.com or call us at 1-307-587-5352 (office hours Monday through Friday, 9am-5pm, Mountain Time, (GMT-7)