ISCTM: Implementing Adaptive Clinical Trials

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Overview

1. Preparing, planning and implementing an adaptive trial
2. Phase 2 Adaptive Trials
3. Getting the data
4. Making the adaptation
5. Reporting to the DMC
6. Supporting the trial logistics

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Background

- I’ve worked with Don Berry and then Berry Consultants for more than 10 years.
- 1998: ASTIN (Stroke) Trial for Pfizer, ground breaking adaptive clinical trial:
  - Bayesian dose response & longitudinal model
  - Frequent update of randomization ratios to different doses
  - Global trial > 50 centers
  - Real time collection of result data
- 2006-9 – Tessella and Berry Consultants:
  - Run >10 trials for a range of large Pharmaceuticals and some smaller Biotechs
  - Phase 2a, Phase 2b, Seamless Phase 2/3
  - Indications including Depression, Diabetes, Schizophrenia, Migraine, Opiate Induced Constipation

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Design Stage

- Develop a software simulator for the design
- Evaluate and refine design
- Create SAP and simulation report
- From simulator code create
  - ‘Recommender’ for use on trial: outputs recommended adaptation based on current trial data
  - ‘Predictor’ simulates forward to end of trial from current data assuming subsequent data is statistically similar to what has been seen already
- Validate (reproduce simulated trial)

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Prepare for Implementation

- Agree how patient endpoint data will be supplied to the recommender e.g. secure file transfer
- Install recommender & predictor on system so that its run whenever data supplied
- Write script to format recommender and predictor output to generate:
  - A new master randomization list sent to central randomization
  - A recommender and predictor report sent to DMC
  - A ‘supply’ predictor report sent to the clinical trial logistics
- Agree how outputs delivered e.g. secure file transfer, email
- Validate system

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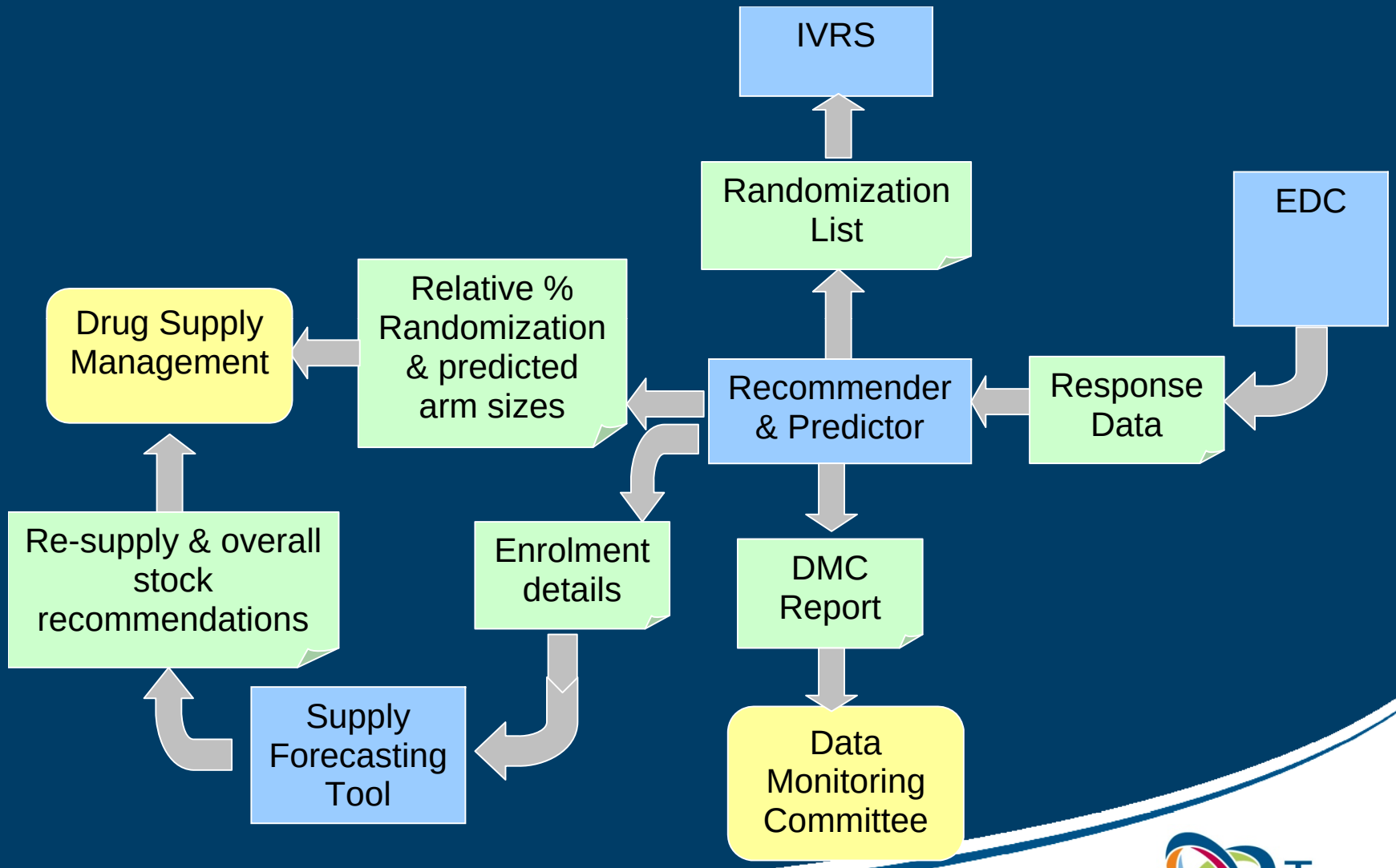
Adaptive Trial Infrastructure



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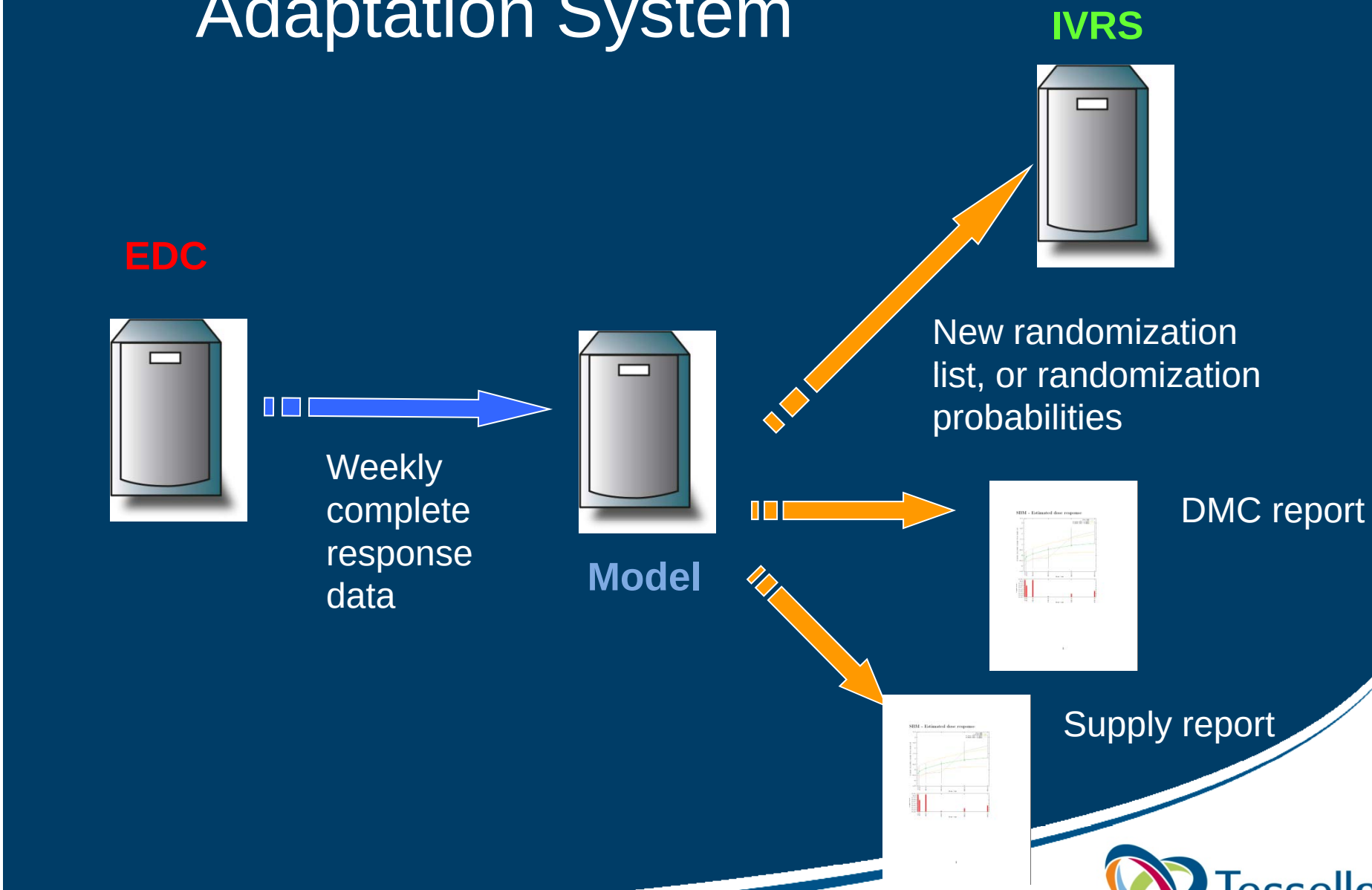
Adaptation System



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Phase 2 Dose Finding Trials

- Endpoint is change from baseline after 1, 2 or 3 months.
- Interim scores available from interim patient visits or from electronic patient diary.
- Score is
  - Simply change from baseline on the endpoint (possibly monotonic)
  - Or a composite of efficacy and penalty for undesirable side effects, so not monotonic
- Treatment arms: Control plus 4 to 8 doses of study drug, plus possible active comparator

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Design

- Model dose response
- Adaptively allocate to doses to find: maximum response, ED90 or MED [MED = Minimum Effective Dose, the lowest dose that beats control by the Clinically Significant Difference]
- Allocate to placebo equivalent to it having a probability of 0.5 of being target
- If probability of having a MED > Target stop for success
- If probability of having a MED < Threshold stop for futility
- Typical study size is from a minimum of 100-200, to a m of 200-400

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Longitudinal data

- Typically 2-3 interim data points available per patient.
- The relationship between these and the final endpoint is modeled using simple linear regression
- Final score for as yet incomplete subjects is imputed from the current score and the linear model
- Additional uncertainty in imputed score accounts for uncertainty due to missing data

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Adaptation

- Start non-adaptively allocating fixed numbers of subjects to selected arms e.g.
  - equal allocation to all
  - half on control, half on top dose
- Update model regularly, creating a new randomization list with:
  - treatment arms in required ratios
  - selected arms dropped
- Report for other adaptations such as stopping the trial, dropping sub-populations

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Response Data

- Supplied as simple file:

```
patient id, visit id, response, toxicity
0001,           1,          7,          0
0002,           1,          4,          0
0001,           2,          8,          0
0003,           1,          5,          0
0002,           2,          3,          1
0001,           3,          9,          0
0003,           2,          6,          0
```

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Alternative to EDC

- Extracting data from some EDC's is only practicable after cleaning – this can add a significant delay to the availability of the data.
- Instead get data directly from lab, investigator or subject
- Use convenient communication: fax, email, phone, text message convenient to fill out (on clip board)
- Reconciled with cleaned EDC data when available
- Use data that agrees or is only in one source
- Send discrepancies back for resolution

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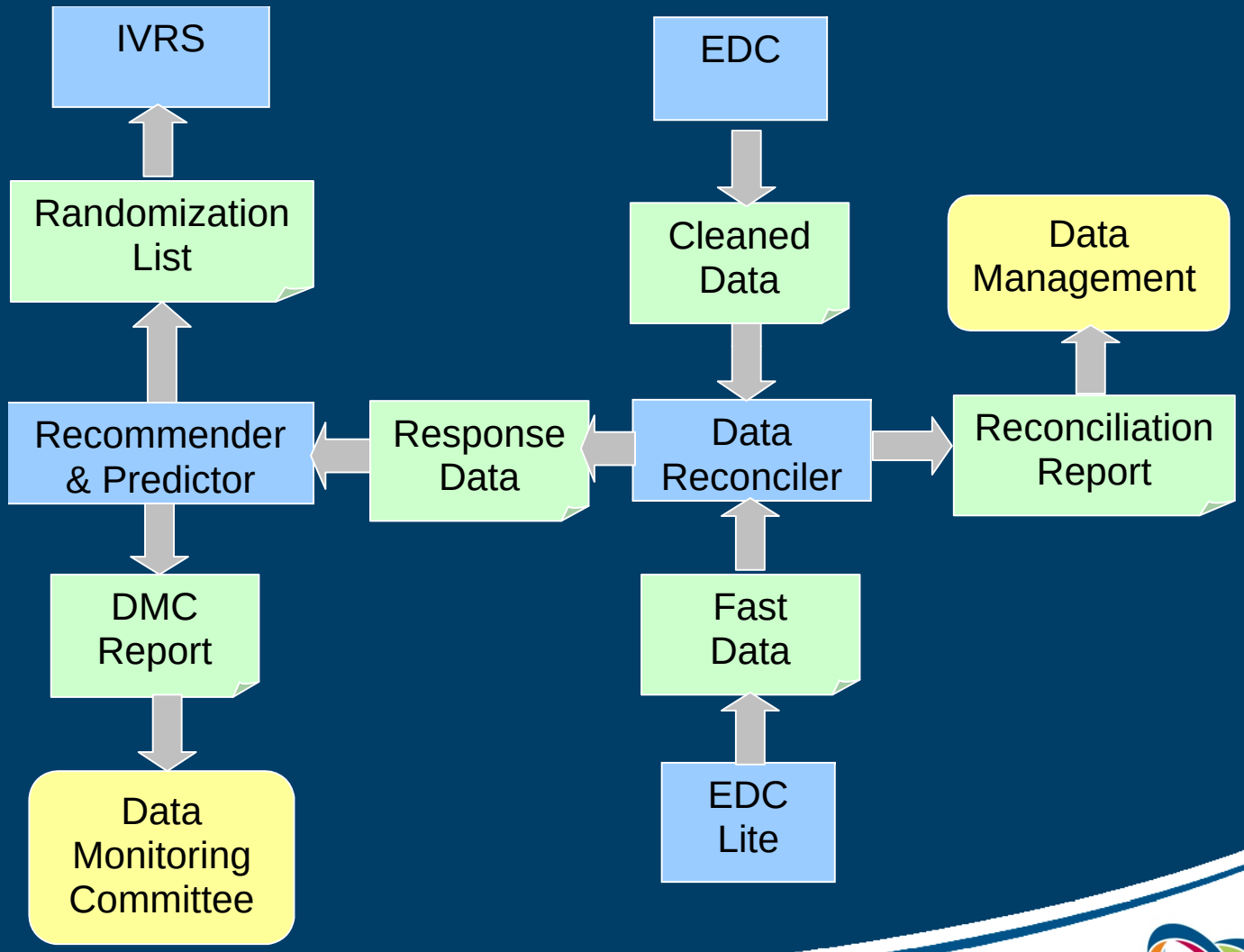
EDC Lite Infrastructure



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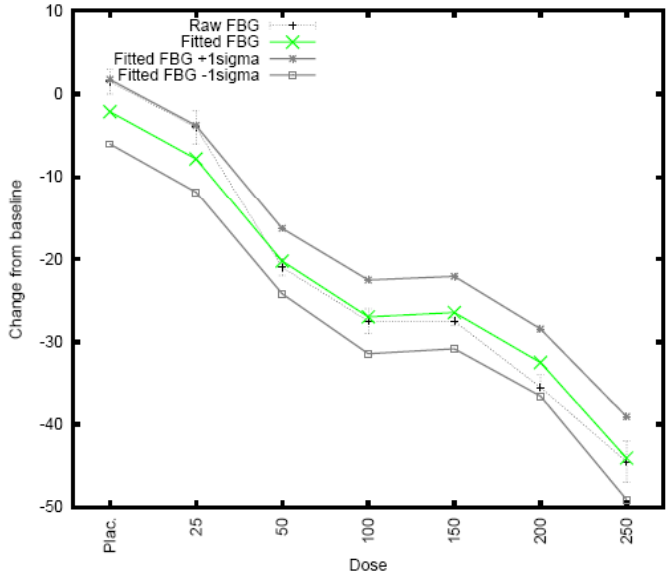
DMC Report

- Current recommendation
- Available data
- Model fit
- Decisions
- Likely outcome (predictive probability)

Response



Subject counts:

	Plac.	25	50	100	150	200	250
Some data	4	4	4	4	4	3	3
Completed	2	2	2	2	2	2	2

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Make up of DMCs

- Phase 1/Phase 2a
  - Member from clinical team on DMC, team unblinded but CRAs and Investigators not
  - No DMC – fully automated!
- Phase 2b
  - Clinical, Biostatistics and Data Management on DMC
  - Possibly all from Sponsor company
  - External when specialist expertise required
- Phase 2/3, Phase 3
  - All members external to
- Possible partially unblinded link to trial supply

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Role of DMC on Adaptive Trials

- Frequent, brief, review of DMC report from model
- Has the model been sent all the available data?
- Has the response data been extracted correctly?
- Does the model appear to have fitted the data correctly?
- Are adaptations being carried out?
- Is the data from the ‘space’ spanned by the scenarios simulated in advance to characterize the design?
- Have any external factors (regulatory, supply, safety, commercial) changed?
- Should the recommended adaptation be adopted?
- Communication

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DMC Actions

- Request explanation of Model behavior
- Request additional simulations
- Request small changes to Model
  - fix error
  - adjust for unexpected circumstances
- Temporary override of adaptation
- Approve recommendation
  - Simple application of arm dropping, new randomization probabilities
  - Stop early: inform steering committee there is a recommendation
  - Pass on recommendation if steering committee want to hear it

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Logistics Support

- Trial simulations used to re-assure supply of the likely worst case scenario of the degree of bias in randomization to any one dose
- Optional supply report each week
  - Combine subjects in screening at each center
  - Current probabilities of randomization
  - To calculate number of different packs of each type required to be 99% sure of supplying randomization
- No forced randomizations

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Logistics Support

- Predictive probability of final trial size and size of each treatment arm
- Current trial state can be loaded into Supply Forecast Tool to simulate trial logistics
  - recommend required re-supplies (depots & centers)
  - judge if overall stock levels are adequate

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Operating Characteristics

- Compare to a fixed design using placebo & 3 study doses possibly with a optional single interim analysis for futility (typically at half way point).
- Adaptive design typically has better alpha and power, more doses, can take undesirable side effects into account and stops earlier if ineffective.
- Correct dose selected more often – typically 65-80% of the time (depending on scenario)
- Post trial analysis on failed trials shows savings of 20-30%
- Post trial analysis on successful trials show better selection of dose and more subjects in dose(s) taken forward

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Example: Seamless PoC and Dose Finding

- Endpoint is change from baseline after 12 weeks, with early observations at 4 and 8 weeks.
- Expected inter-patient variability in endpoint scores is expected to have a SD of ~5 points
- The target improvement is 2 points
- Treatment is placebo or one of 6 doses of study drug.
- The target is to find the MED and ED90.
- Patient recruitment will reach ~30 subjects per month

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Model

- Final dose response is modeled using a first order NDLM
- Longitudinal data is modeled using simple linear regressions
- Non-informative priors are used
- Missing values are drawn from the posterior probability distribution – assuming missing at random

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Decision Rules

- Minimum efficacy is a reduction from baseline of 1 points.
- Success is >80% probability that there is a greater reduction from baseline score at ED90 than placebo, by 2 points or more.
- Failure is >95% probability that no dose has the minimum efficacy.
- Maximum study size is 400.

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Adaptive Allocation Rules

- Initially 5 subjects are randomized to each study arm
- There after the randomization is modified to allocate subjects to arms in proportion to the probability that they are the ED90 or the MED dose.
- Model updated every 2 weeks
- Subjects are allocated to placebo with a constant probability of 20%.

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Operating Characteristics

- Alternative fixed design is a PoC study (N=200) followed by a standard Parallel Group phase 2 (N=500)
- The adaptive design, from simulation:
  - mean study size 200 under the Null Hypothesis, alpha ~ 0.05
  - so cost if compound ineffective is equivalent to PoC trial
- Tests 2 more doses
- Uses 300 fewer subjects
- Better characterization of MED & ED90
- If successful saves 18 months and $10M

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