Writing Simulators: “There’s more to it than the stats analysis” – advice to statisticians from a computer programmer

Berry Consultants
Statistical Innovation

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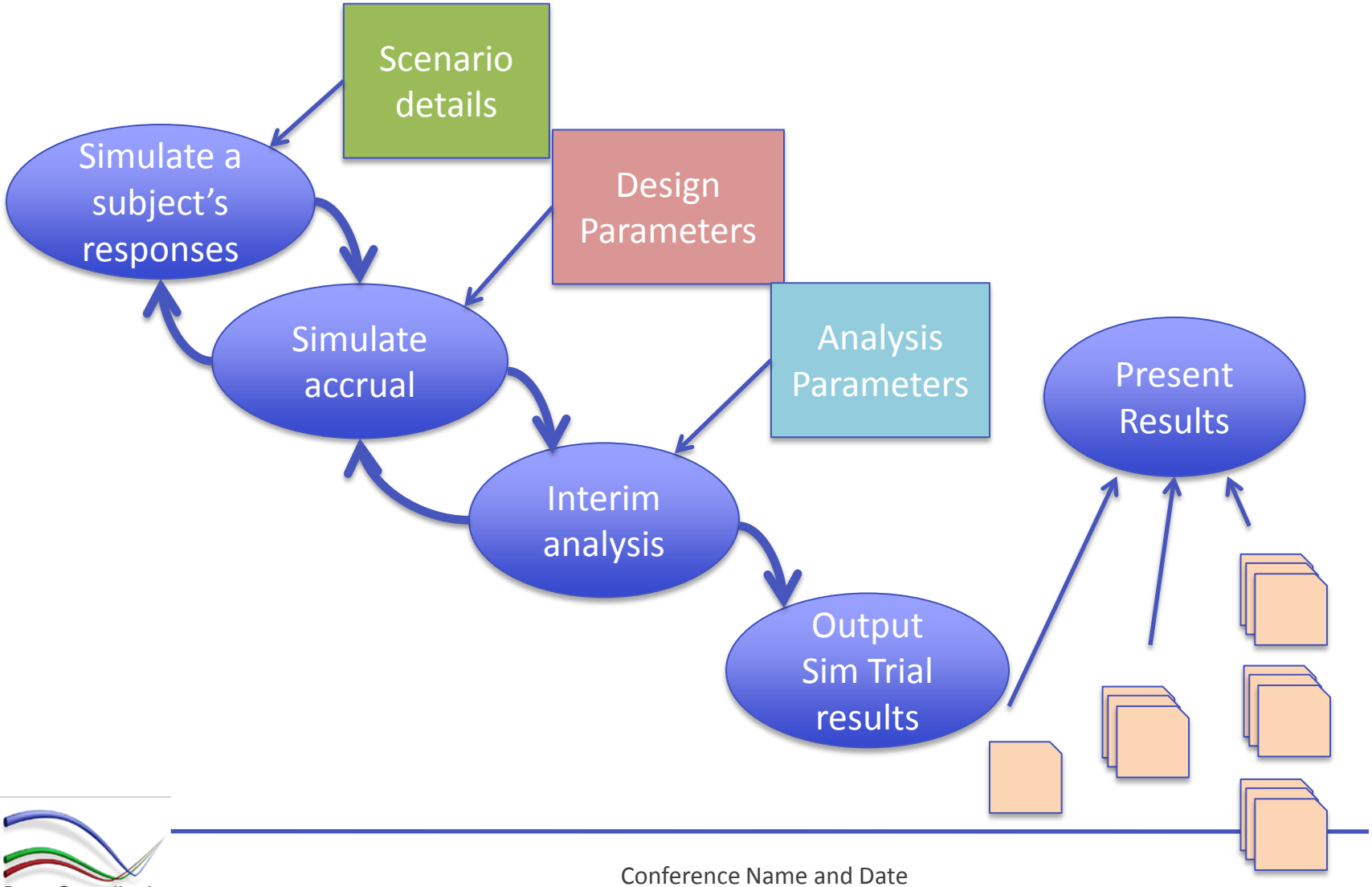
Writing a Clinical Trial Simulator

- Background:
  - Worked in SW since 1979
  - Working on trial simulators since 2002: Pfizer, MD Anderson, Wyeth, Eli Lilly ... FACTS^{tm}
  - Worked on R simulations for ISCTM & DIA Adaptive Program Working Group

The Problem

- The simulation results need to be trusted
- The results need to be available when required
- The simulation will need to change as the plan changes
- You will need to back months later and remember where results came from (reproducibility)

Analysis -> Simulation



Analysis -> Simulation

- The whole thing has got bigger
- But the stuff round the analysis is just “book keeping”
- The chance of making an error in software is not strongly correlated to how intellectually challenging that s/w is. (Possibly negatively correlated!)
- If the stuff around the analysis (which you will not find so interesting) is not given the time and attention it requires you will fail

Failure …

- The results will not be trusted
- The results will not be available on time
- The simulation will not be able to be easily adapted as the plan changes
- Months later it will not be clear exactly how simulation results were generated

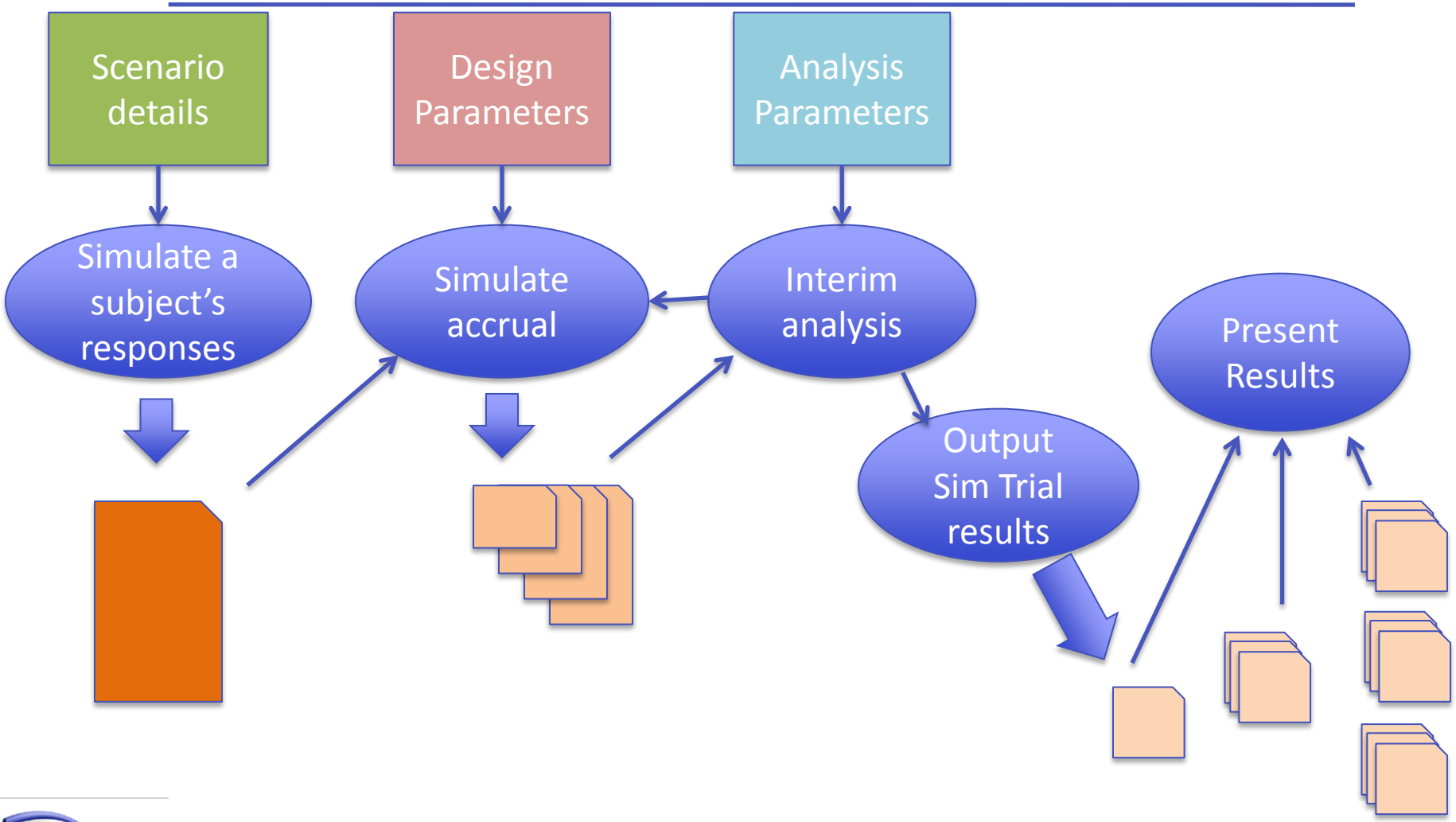
Truisms

- The simulations will be run and re-run far more often than you expected
- The simulations will have to be modified far more often than you expected
- Successful software is run for a lot longer than you expected
- But most software is not successful…..

How to tackle this

- Modular approach
- Start Simple
- Test as you go
- Retain intermediate results
- Attend to simulation hygiene

Modular Approach



Benefits of modularity

- Can build and test a stage at a time
- Can run a stage at a time and re-run a stage
- When we have to make changes we will often be able to isolate them to a particular stage
- Start with a **simple** analysis stage and get everything else working first.

Start Simple

- Postpone the intellectually challenging (a.k.a interesting) part of the project to later
- Develop the “book keeping” code first
- Give the BK code the attention it requires
- Get end-to-end results with simple analysis
- Incrementally build up the interesting part of the project - compare results with each increment.

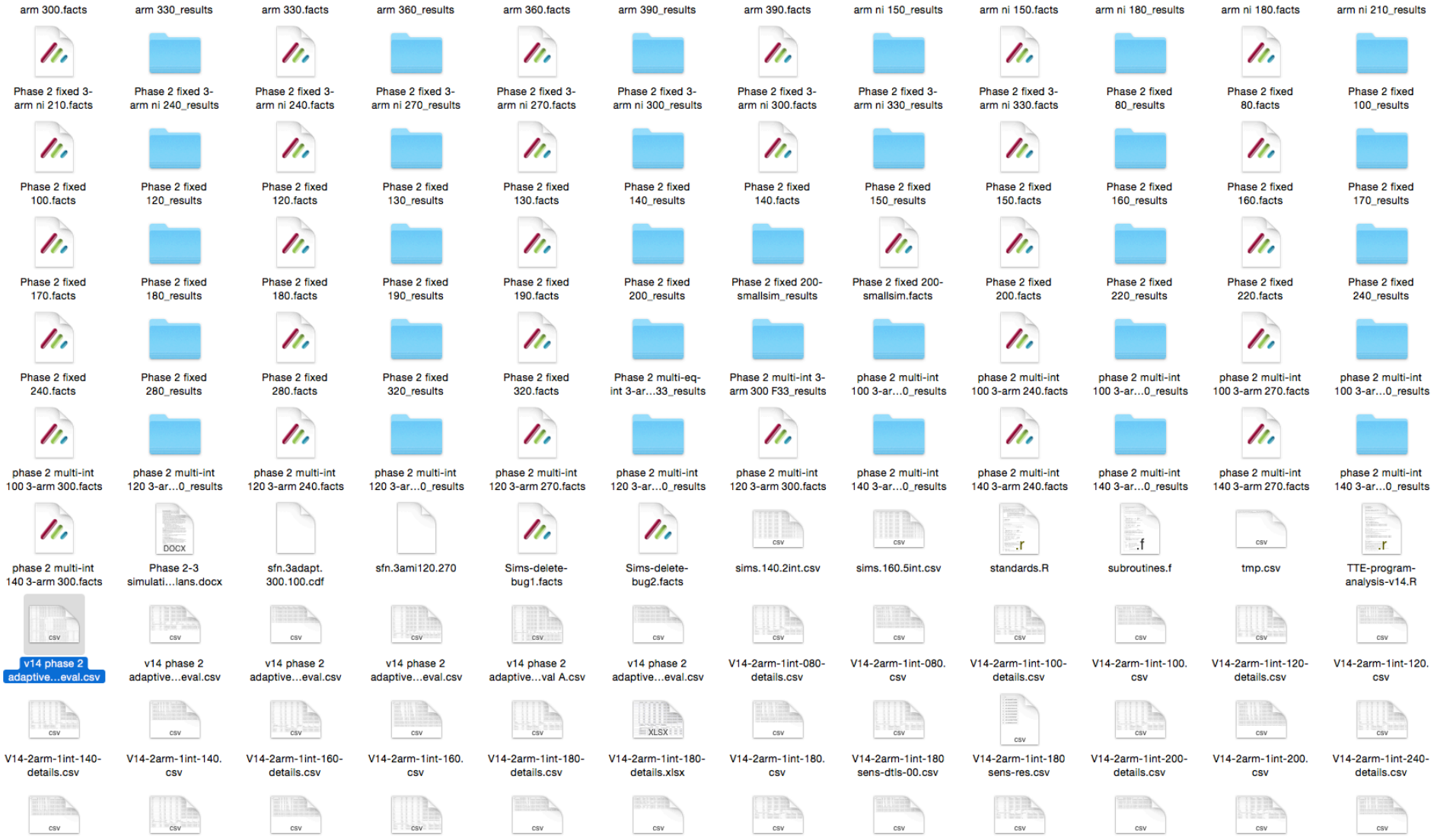
Testing

- Test components individually
- Test Single analyses first (not averages over many sims)
- Be especially suspicious of early “good” results!
- Chase down any discrepancy, no matter how minor

Retain intermediate results

- Be able to write out
  - Simulated subjects
  - Sampled subjects per simulation
  - All interims
- Be able to use the analysis part of the simulation on real data (don't want to have to re-implement the analysis)

Hygiene


arm 300.facts
arm 330_results
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arm ni 150_results
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Phase 2 fixed 3-arm ni 210.facts
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Phase 2 fixed 120_results
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Phase 2 fixed 130_results
Phase 2 fixed 130.facts
Phase 2 fixed 140_results
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Phase 2 fixed 150_results
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Phase 2 fixed 160_results
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phase 2 multi-int 140 3-arm 300.facts
Phase 2-3 simulati...lans.docx
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sfn.3ami120.270
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Sims-delete-bug2.facts
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sims.160.5int.csv
standards.R
subroutines.f
tmp.csv
TTE-program-analysis-v14.R
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v14 phase 2 adaptive...eval.csv
v14 phase 2 adaptive...eval.csv
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v14 phase 2 adaptive...eval.csv
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V14-2arm-1int-160-details.csv
V14-2arm-1int-160.csv
V14-2arm-1int-180-details.csv
V14-2arm-1int-180-details.xlsx
V14-2arm-1int-180.csv
V14-2arm-1int-180 sens-dtls-00.csv
V14-2arm-1int-180 sens-res.csv
V14-2arm-1int-200-details.csv
V14-2arm-1int-200.csv
V14-2arm-1int-240-details.csv

Hygiene

- Organize results (a folder per run?)
- Store code & inputs as well as outputs –
  - Reproducibility
  - Group all parameters in the code write them out to a file
  - For important simulation exercises

Performance

- For type-1 error you will need many sims (100,000)
- But for design comparison & optimization you need fewer – we want 'significant' improvement due to large difference not small SE!
- But incredibly powerful to be able to run 'indicative' number of sims (100-1,000) during a meeting, i.e. in a few minutes.
- Speed of simulation will be important!