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Shaping the Future of
Drug Development

Case study: how promising is the VALOR trial for the future of adaptive designs?

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Key points

VALOR was a successful promising zone design

- Despite failing on the primary endpoint, the totality of data suggested benefit for Vosaroxin in relapsed/refractory AML

Adaptive uSSR and PZD are now indispensable tools in a trial statistician's toolbox

- Risk mitigation
- Staged investment

Important lessons learned from implementation

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Case Study: VALOR Trial for AML

Background

Therapy for relapsed or refractory AML generally unsatisfactory; no approved drugs; dismal prognosis

Vosaroxin, a first-in-class anticancer quinolone derivative, had previously been studied in a single arm Phase 2 study

Trial Design

Vosaroxin and **A**ra-C combination eva**L**uating **O**verall Survival in **R**elapsed/refractory AML

Phase 3, double-blind, placebo-controlled, multinational trial with Overall Survival (OS) endpoint

Two-stage Promising Zone Design

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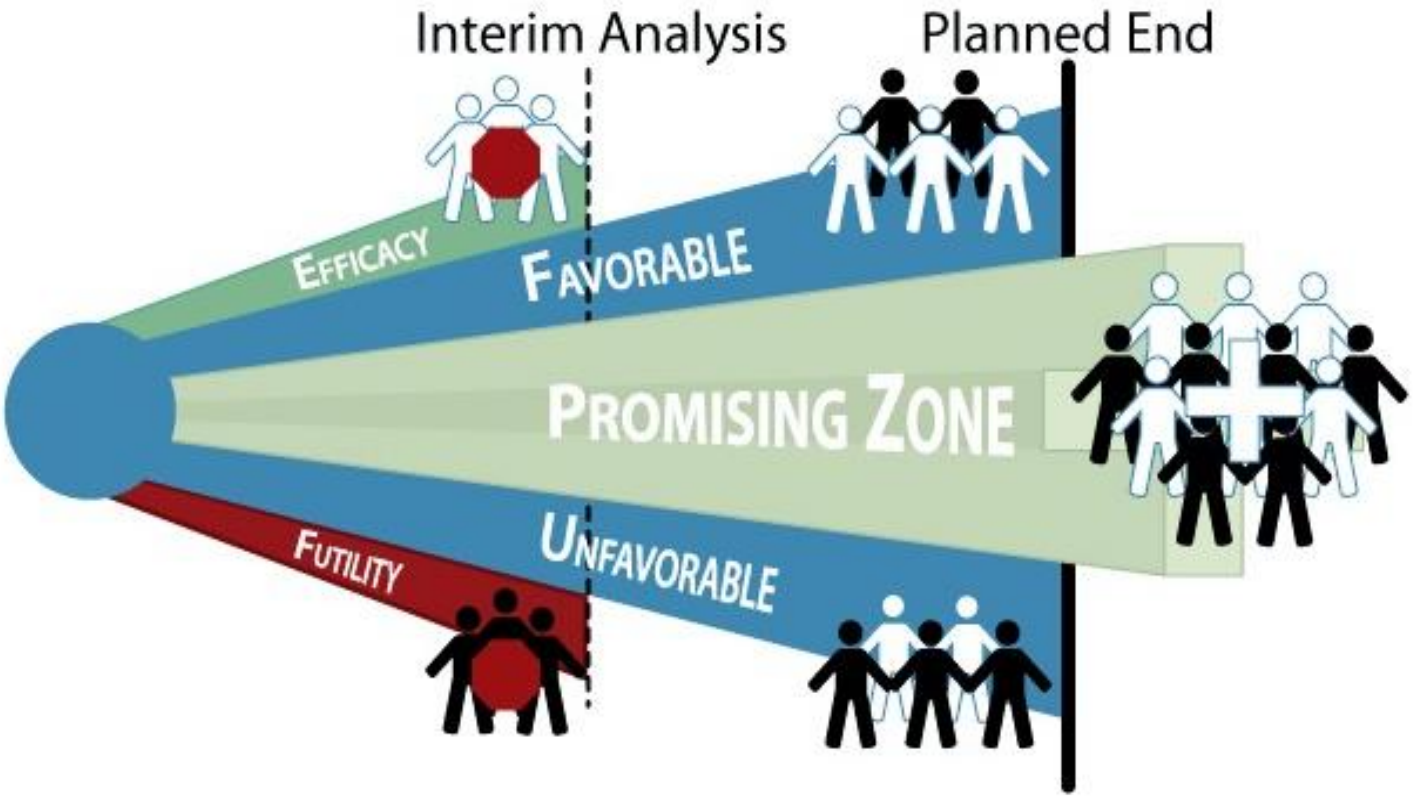
Promising Zone Design

(Mehta & Pocock, 2011)



Efficacy zone (OBF)
One-sided p=0.0015

Favorable zone
(CP ≥ 0.9).

Promising zone
(0.3 ≤ CP < 0.9);

Unfavorable zone (0.1 <CP < 0.3);

Futility zone
(CP ≤ 0.1)

Interim Analysis at 187 Events
Planned End at 375 events
Maximum number of Events: 561

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Design benefits

Mitigate uncertainty in design assumptions

Respond flexibly to accumulating data

Upfront sample size investment can be modest

Additional investment only made if interim results are promising

If that happens, chances of success are dramatically increased

Adaptive financing: more flexibility to balance risk, cost, and duration of capital commitment

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A Strategy of Staged Investments

Design realistically up-front. Power study to detect HR=0.71 (requires 375 events; 450 subjects @ 19/month)

One interim analysis after 50% information (187 events)

- Stop early if overwhelming evidence of efficacy (LD-OBF)
- Stop early for futility if low conditional power
- Increase number of events, sample size and (if possible) rate of recruitment at the interim if results are promising

Control type-1error by using Cui, Hung and Wang (1999) weighted statistic modified for survival data

Evaluate operating characteristics of design by simulation

Key idea: Milestone-Driven Investment
Invest additional resources and re-power the study to detect HR=0.77 only after seeing interim results

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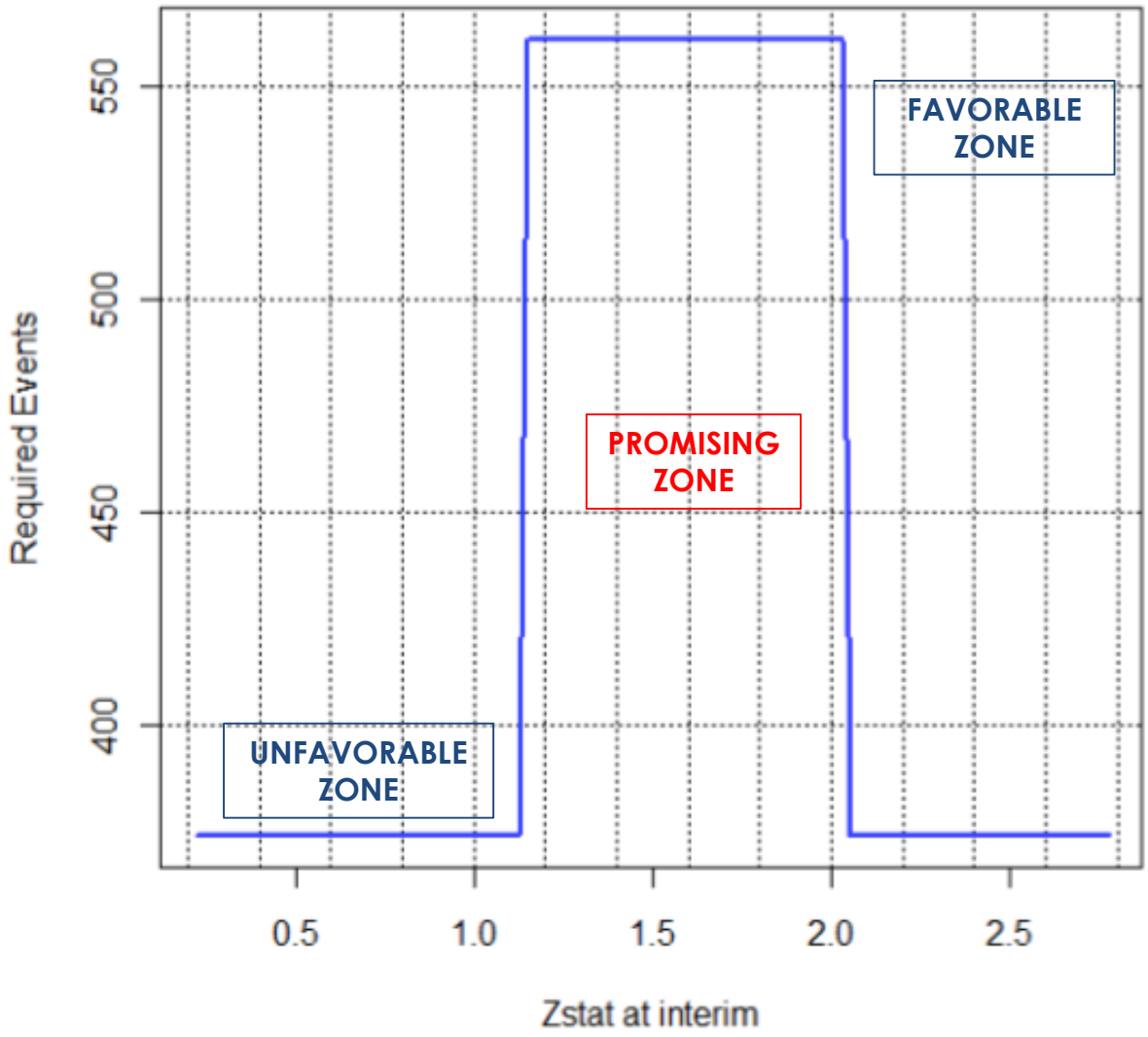
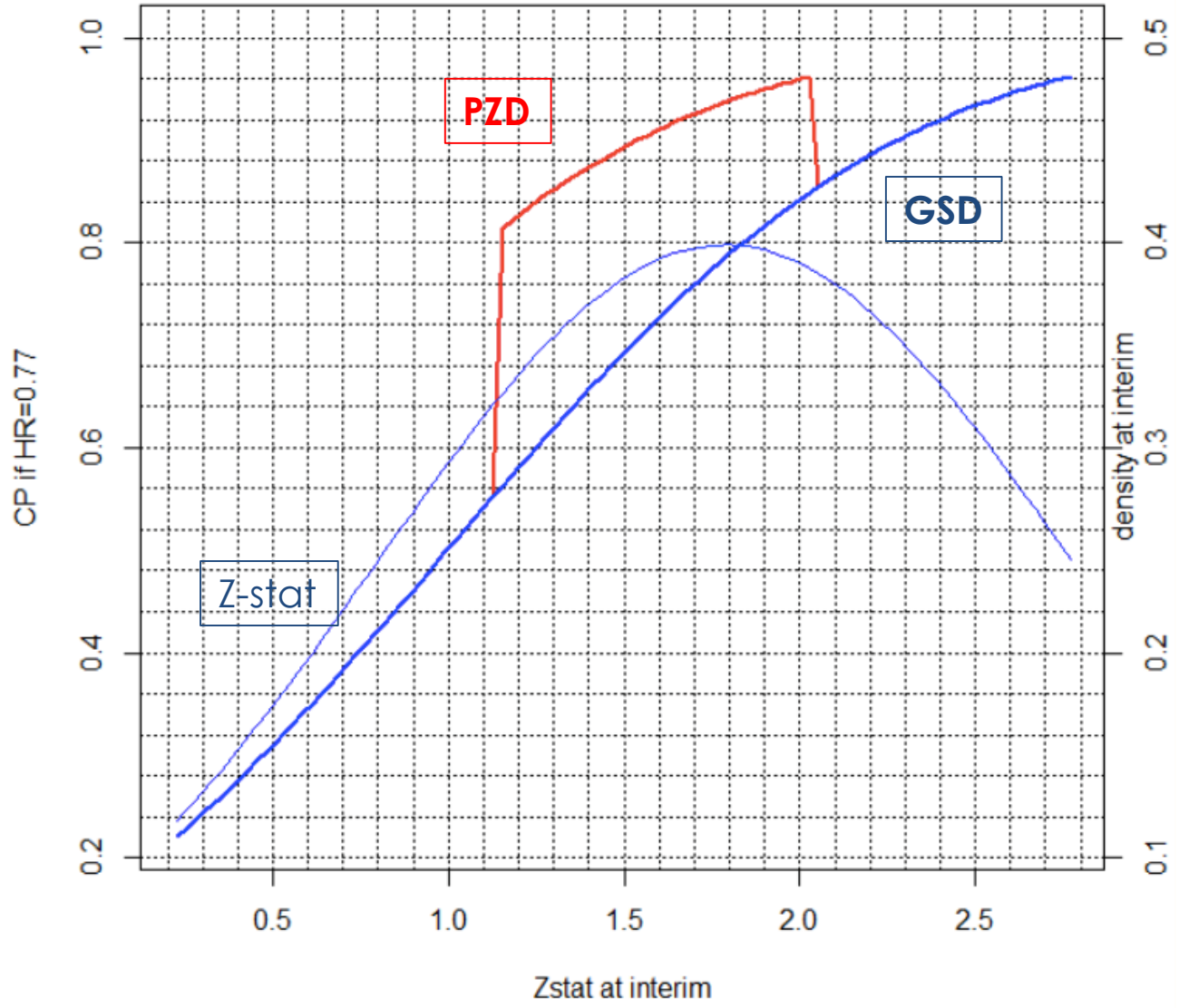
A Simple Interim Adaptation Rule



Conditional Power Boost



Regulatory considerations

Briefing document with SAP is crucially important

Justify why adaptive approach is necessary

Describe the statistical methodology and details for control of type-1 error

Describe the promising zone decision algorithm

Provide simulation results under various scenarios

Provide the data monitoring committee (DMC) charter

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Operational considerations

Establish excellent SOPs:

- Document "who saw what and when"
- Document who has had full access to details of the adaptive algorithm
- Document all data and programs used for the interim analysis

Appoint a Data Monitoring Committee

Appoint an independent statistical center to perform the interim analysis for the DMC

Educate investigators, analysts, and investors

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Avoidance of Operational Bias

Must provide auditable evidence that SSR was strictly followed and based only on the pre-specified decision rule

Ensure that firewalls were in place to protect unblinded analyses

Show evidence that Sponsor was not involved in ISC and DMC interactions and was not exposed to unblinded IA results

VALOR used ACES, a secure, web-based system to streamline the interim analysis process:

- DMC portal for secure centralized storage of documents
- Analysis programs loaded and run from within
- Non-invasive audit-trail available for review

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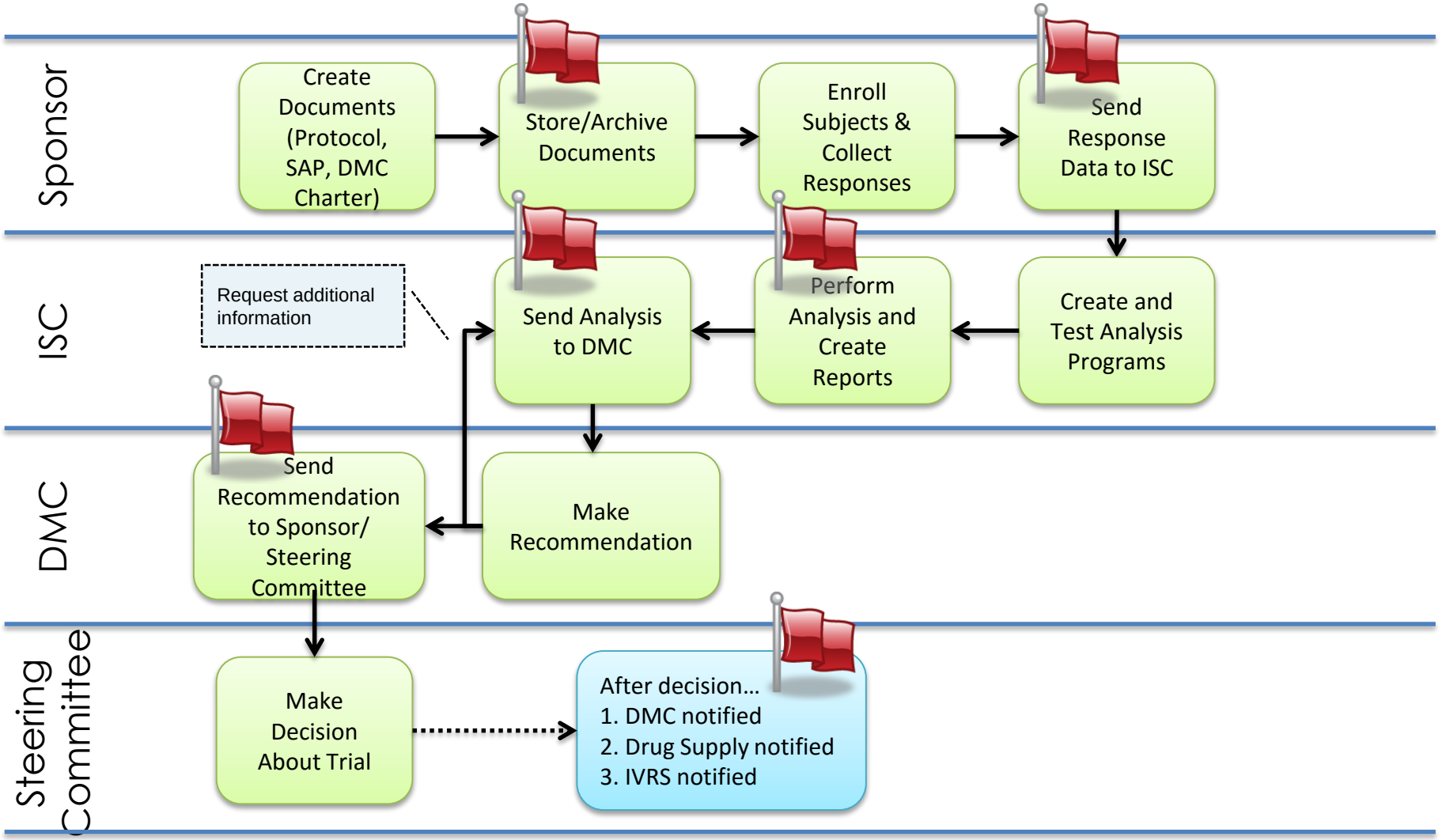
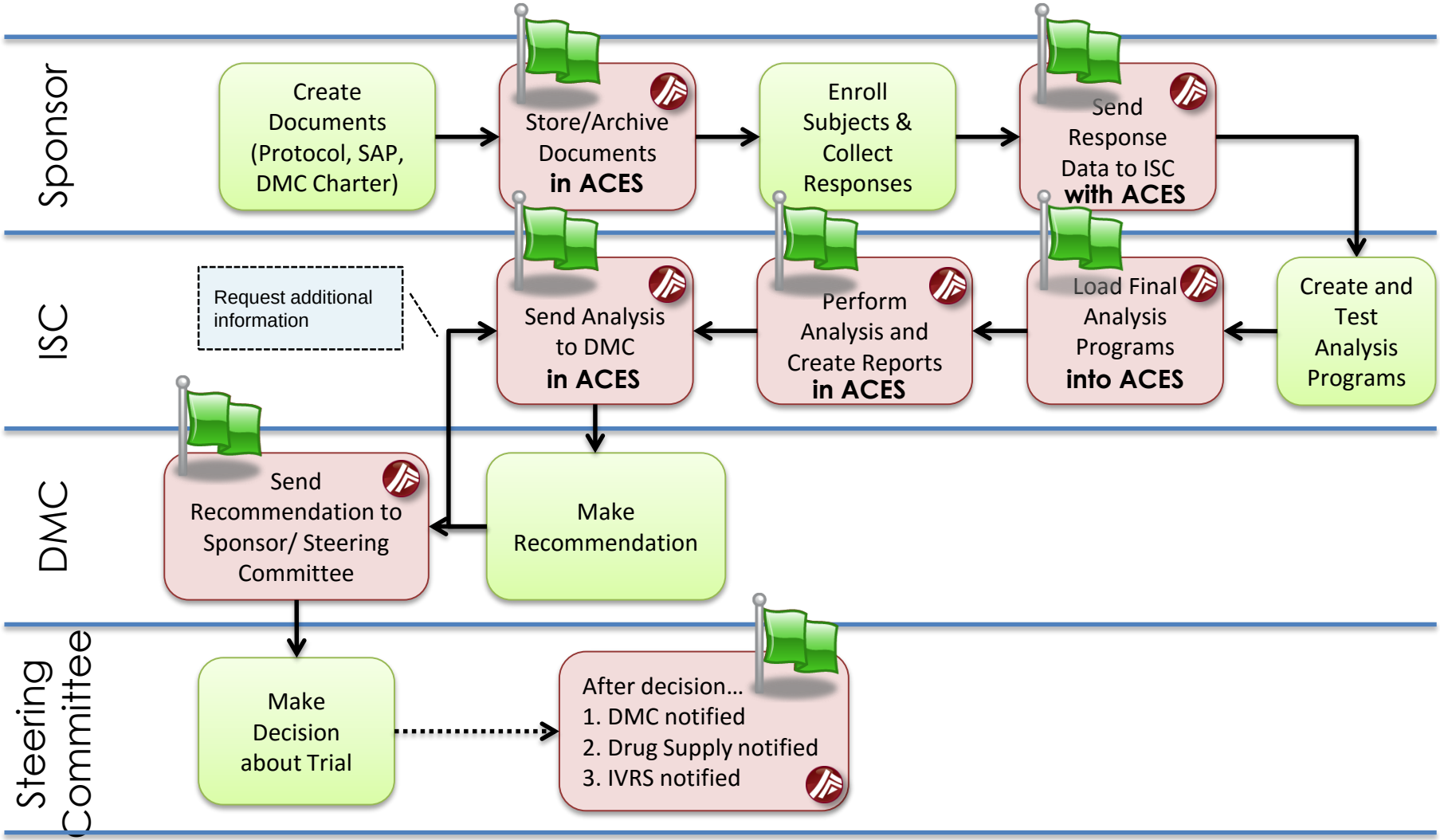
Traditional Process



ACES Process



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Final results

Interim Analysis

- Interim analysis conducted with 173 events, rather than 187 as planned
  - HR was 0.76
  - Conditional power was 82% (in the promising zone)
- Both sample size and events were increased by 50%

Final Results

- Primary endpoint Overall Survival:
  - 7.5 months on Vosaroxin vs. 6.1 months on Placebo
  - Unstratified results: HR = 0.87, p = 0.06
  - Stratified results: HR = 0.83, p = 0.02
- Single secondary endpoint, Complete Response Rate: 30.1% Vosaroxin vs. 16.3% Placebo, $p < 0.0001$

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Lessons learned

PZD and uSSR are an essential part of the trial statisticians' toolbox

Engage regulatory authorities early on

Have a strong rationale for adaptation

Demonstrate type-1 error control

Implement safeguards to control for operational bias:

- Adaptation rules as appendix to DMC charter
- Appoint an independent statistician who can explain design subtleties to DMC members
- Use technology and processes to ensure maintenance of the blind and trial integrity

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Main references

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- Mehta, C.R., and Pocock, S.J. (2011). Adaptive increase in sample size when interim results are promising: a practical guide with examples. *Stat Med*. **30**: 3267-84.
- Ravandi, F., et al. (2012). VALOR, an adaptive design, pivotal phase 3 trial of Vosaroxin of placebo in combination with Cytarabine in first relapsed or refractory acute myeloid leukemia. ASCO poster. http://www.sunesis.com/data-pdf/595/sunesis-valor-vosaroxin-201206-ASCO.pdf
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Thank You Very Much

Any Questions?

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