Proposal For a Platform NASH Trial

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Key Challenges in NASH Clinical Development

- Natural history of NASH not yet well understood
  - Majority of data come from retrospective analyses and meta-analyses of smaller, prospective studies
- Current requirement of liver biopsy for diagnosis and prognosis
  - Absence of accepted biomarkers that can be used in lieu of liver biopsy for clinical development
- Limited number of pre-identified patients likely, in part, given requirement for liver biopsy and lack of approved therapies
- Many companies have entered this drug development space

NASH - Competitive Landscape

Class	Drug	Company	Status
FXR agonist	Obeticholic acid	Intercept	III (Breakthrough)
Dual PPAR α/delta agonist	Elafibranor	Genfit	III (Fast Track)
CCR2/CCR5 inhibitor	Cenicriviroc (CVC)	Allergan	III (Fast Track)
Fatty acid/bile acid modifier	Aramchol	Galmed Pharmaceuticals	II/III (Fast Track)
ASK1 inhibitor	Selonsertib	Gilead	III
GLP-1	Semaglutide	Novo Nordisk	II
Bovine colostrum/anti-LPS Ab	IMM-124E	Immuron	II
FGF19	NGM282	NGM	II
FGF21 (peg)	BMS-986036	BMS	II
Galectin-3 inhibitor	GR-MD-02	Galectin Therapeutics	II; Fast Track
Caspase inhibitor	Emricasan	Conatus	II; Fast Track
ACC inhibitor	GS-0976	Gilead	II; Fast Track

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REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

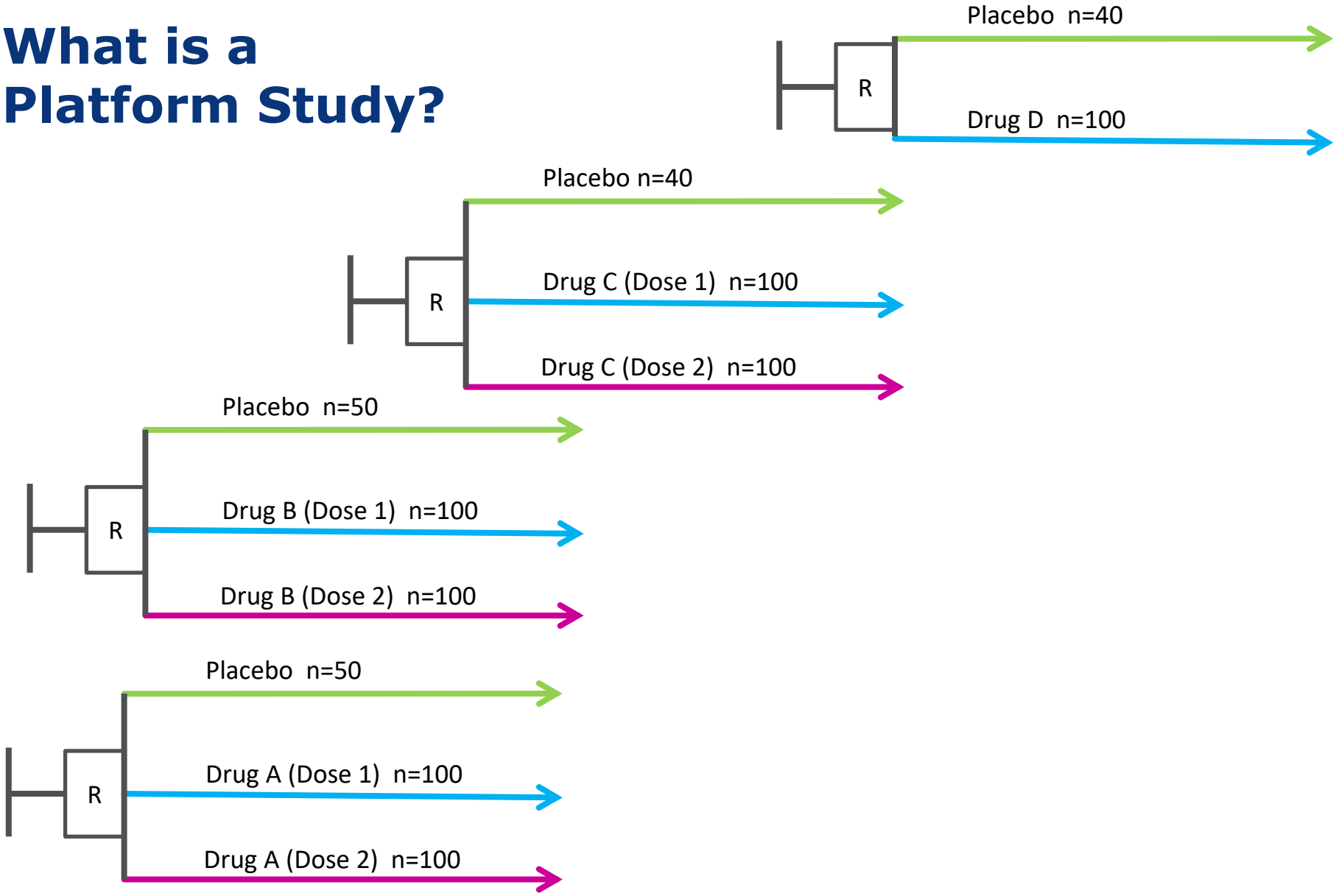
Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

Platform study: "To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm"

Existing platform studies: I-SPY2 (breast ca), Lung-MAP (NSCLC), EPAD (Alzheimer's Dz), GBM AGILE (glioblastoma)

What is a Platform Study?



General Characteristics of Traditional and Platform Trials

Table. General Characteristics of Traditional and Platform Trials[a]

Characteristic	Traditional Trial	Platform Trial
Scope	Efficacy of a single agent in a homogeneous population	Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous
Duration	Finite, based on time required to answer the single primary question	Potentially long-term, as long as there are suitable treatments requiring evaluation
No. of treatment groups	Prespecified and generally limited	Multiple treatment groups; the number of treatment groups and the specific treatments may change over time
Stopping rules	The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment	Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)
Allocation strategy	Fixed randomization	Response-adaptive randomization
Sponsor support	Supported by a single federal or industrial sponsor	The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination

[a] Platform trials and similar trials may also be called basket, bucket, umbrella, or standing trials.

Berry et al. *JAMA* 2015; doi:10.1001/jama.2015.2316

NASH Platform Study:
Efficiently Addressing Clinical Development Issues

- Scientific
  - Better definition of NASH natural history via analysis of common placebo control group
  - Standardized collection of clinical endpoints, liver biopsy, and non-invasive biomarkers across large # of subjects accelerates goal of developing/validating non-invasive biomarkers
  - Adaptation of platform to prioritize recruitment of compounds showing significant benefit
  - Centralized and shared governance structure (SC, DMC, centralized liver biopsy reading, adjudication committee) provides consistent oversight and reduces start-up times and cost

- Regulatory
  - HA approval of core NASH platform study may allow for more rapid study start-up for each compound entering platform study

NASH Platform Study:
Efficiently Addressing Clinical Development Issues

- Operational
  - Rapid study start-up of qualified sites trained on platform study with oversight by 1° Ethics Committee
  - Pre-identification of potential study subjects reduces recruitment time
  - Overall reduced screen failure rate as subjects ineligible to enroll for one compound potentially eligible for other compounds (benefit to subjects/PIs)
  - Shared common placebo control group reduces # of subjects needed for enrollment for each compound in platform (also improves odds that subject receives active therapy)

Status:

- NASH platform study part of broader Innovative Medicines Initiative 2 (IMI2) proposal of platform studies in depression, IBD, tuberculosis, and multiple myeloma
- Non-binding scientific interest in platform expressed by 8+ companies
- Endorsement by European Federation of Pharmaceutical Industries and Associations (EFPIA) leadership involved with Innovative Medicines Initiative 2 (IMI2) program
- Submission of proposal to IMI postponed to Call 15 (~3 month delay; ~June 2018)

How to Set-up a NASH Platform Study

- Establish pre-competitive collaborative biotech/pharma group to work with KOLs and Profession Societies to agree on scientific objectives
  - Identify academic and pharma champions to lead effort
- Design platform study
  - Selection of compounds
  - Patient type
  - Establishment of cohort of pre-identified subjects
  - Study phase (2 and/or 3/4)
  - Duration of study
  - Primary and secondary endpoints
  - Biomarkers (imaging and blood/urine samples) and timing
  - Inclusion/exclusion/discontinuation criteria
  - Statistics: randomization, powering, and analysis plan
  - Health authority input
  - Ability for each compound to tailor study according to compound/target needs
  - **MUST CREATE A MORE EFFICIENT DRUG DEVELOPMENT PARADIGM THAN CURRENT STANDARD OF NASH DRUG DEVELOPMENT**
- Need to define operational details and *sources of funding*
  - ARO/CRO
  - # of sites and identify specific sites
  - Central IRB/EC, IDMC, Steering Committee

Conclusions:
NASH Platform Study

- Helps advance understanding of NASH and NASH drug development
  - Natural history, source of data for biomarker validation (eg for LITMUS and NIMBLE), more efficient drug development in already crowded development space

- Requires collaboration across biotech, pharma, and academia
  - Needs to result in shorter drug development timelines (eg IRB/EC/HA approvals, study start-up, operational consistency, etc.) and reduced drug development costs

- Needs appropriate and sustainable source of funding
  - Likely greatest near-term challenge given available pharma resources and associated opportunity costs
  - Potential to offset costs via IMI in-kind funding, other sources of funding (including governments, professional societies, private philanthropy)