Expediting Clinical Development for Cell and Gene Therapies ---
Applying Master Protocol Concept in Early-Phase Trials

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Outline

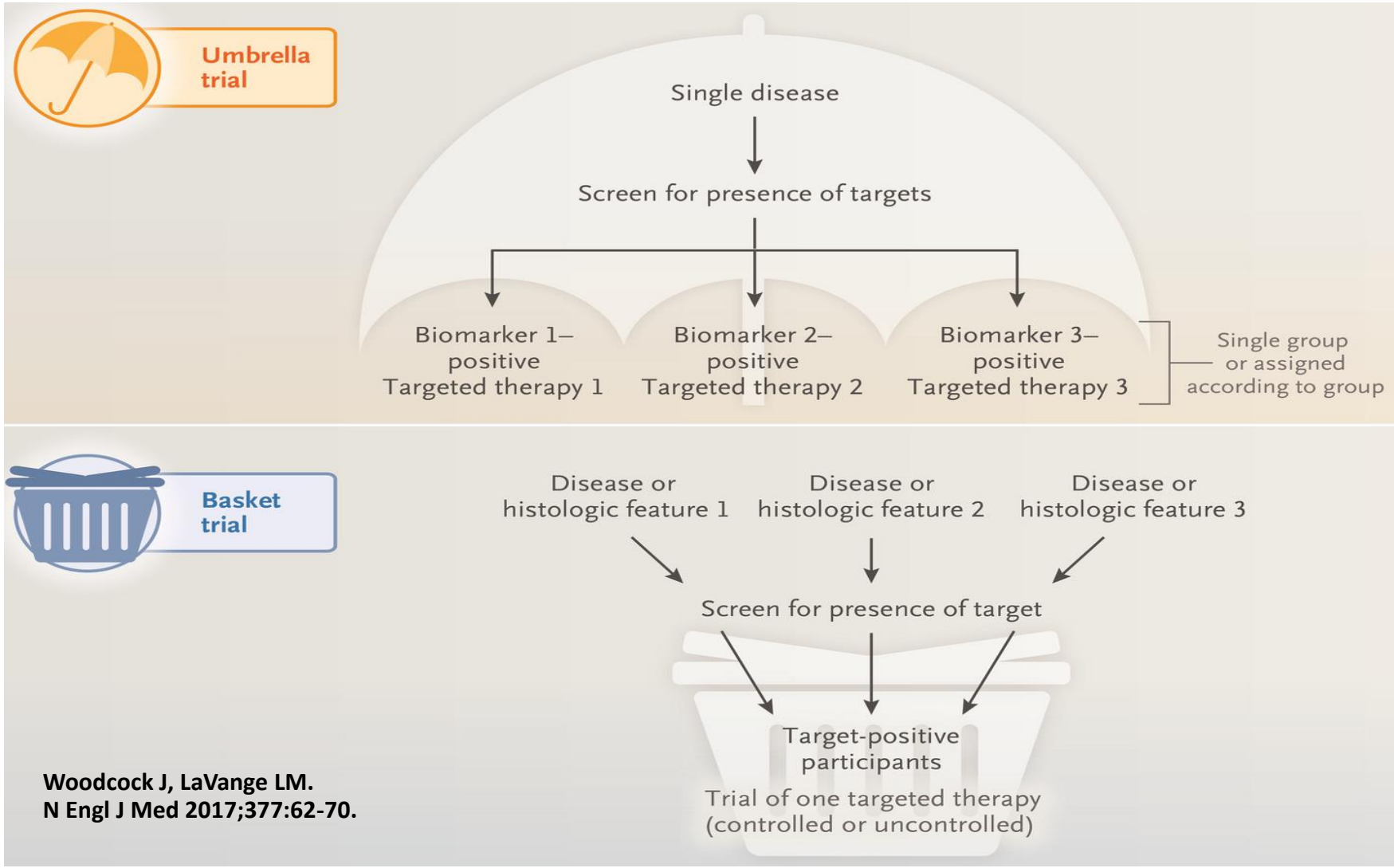
- Master Protocol (MP)
  - Concept
  - Type
  - Advantage
  - Challenges
- Applying MP concept to expedite the CGT development in early-phase trial
- Summary

Master Protocol --- Concept

- A master protocol is defined as an overarching protocol designed with multiple objectives that involve coordinated efforts to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structure.

- Can be exploratory or confirmatory.

Master Protocol --- Types



Woodcock J, LaVange LM.
N Engl J Med 2017;377:62-70.

Master Protocol --- Advantages

Areas of Innovation

Infrastructure

- Common screening platform for biomarker identification
- Governance
  - Steering committee
  - Adjudication committee
  - Data monitoring committee
  - Central institutional review board
- Trial networks and clinical centers
- Processes
  - Randomization
  - Data and safety capture and management
  - Quality-control oversight

Trial Design

- Adaptive randomization and other adaptive design features
- Longitudinal modeling to determine probabilities of success or failure
- Shared control patients
- Natural-history cohort
- Biomarker qualification

Woodcock J, LaVange LM.
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Master Protocol --- Challenges

- Difficult to attribute adverse events to a given investigational product if an arm contains more than one investigational product or in combination with other approved products

- Prone to “over-interpret” the findings from exploratory comparisons across investigational arms, leading to delays in drug development

Innovations and CGT Product Changes

- Continuous need for innovation
- Product change inevitable, leading to different versions of a CGT product but still related to the original product
- Regulatory challenge for industry:
  - Different products, albeit related, need an IND for each product with all components
  - May be burdensome, not cost-effective, and inefficient

“Parent - Child IND” Concept*

- Original Product (e.g., CAR T construct) --- Parent IND
- Closely-related T-cell-based candidates or related manufacturing process alterations --- Child INDs
- Child INDs cross-referencing parent IND

* https://www.focr.org/sites/default/files/pdf/Friends_Cellular_Therapies_White_Paper.pdf?eType=EmailBlastContent&eId=7e1fee3f-287e-4dc4-89ac-e8548460e7fd

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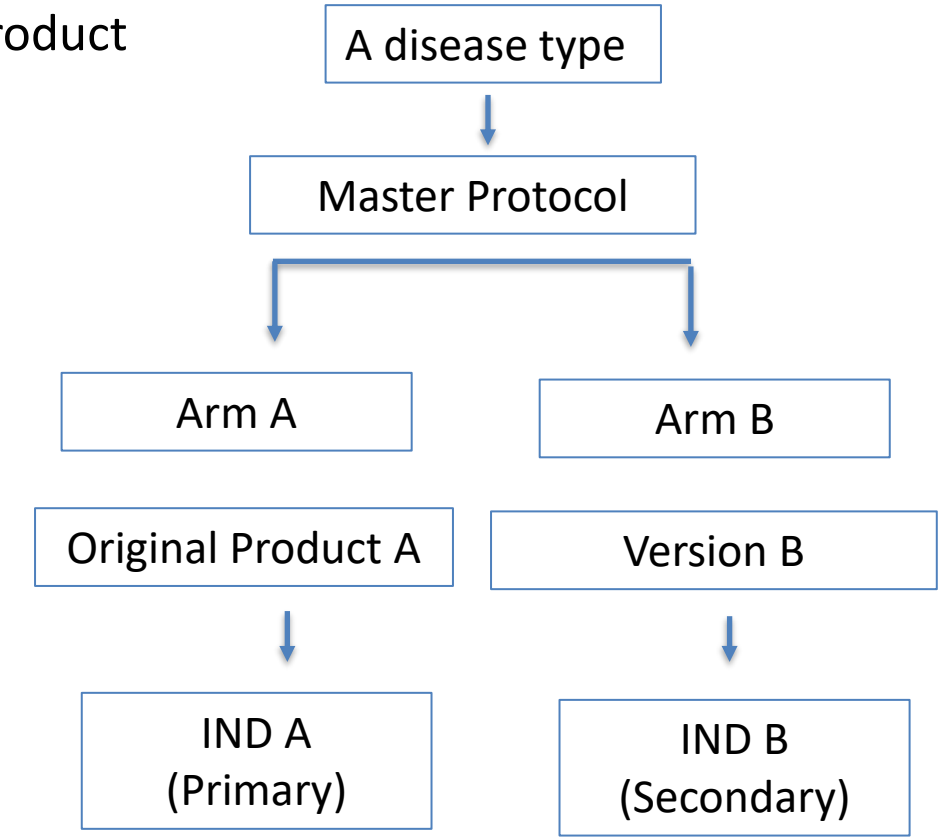
For multiple versions of a CGT product



Regulatory implications:

- Primary IND A containing:
  - all clinical information, e.g.,:
    - clinical protocol
    - investigator brochure
    - informed consent form
    - Form FDA 1572
  - CMC, P/T modules for IND A
  - Cross-reference CMC, P/T information of product version B to IND B
- Secondary IND B containing:
  - CMC, P/T modules for IND B
  - Cross-reference clinical information to IND A
- Need to have pre-assigned IND numbers before submission
- Sponsor having full access to information of all INDs

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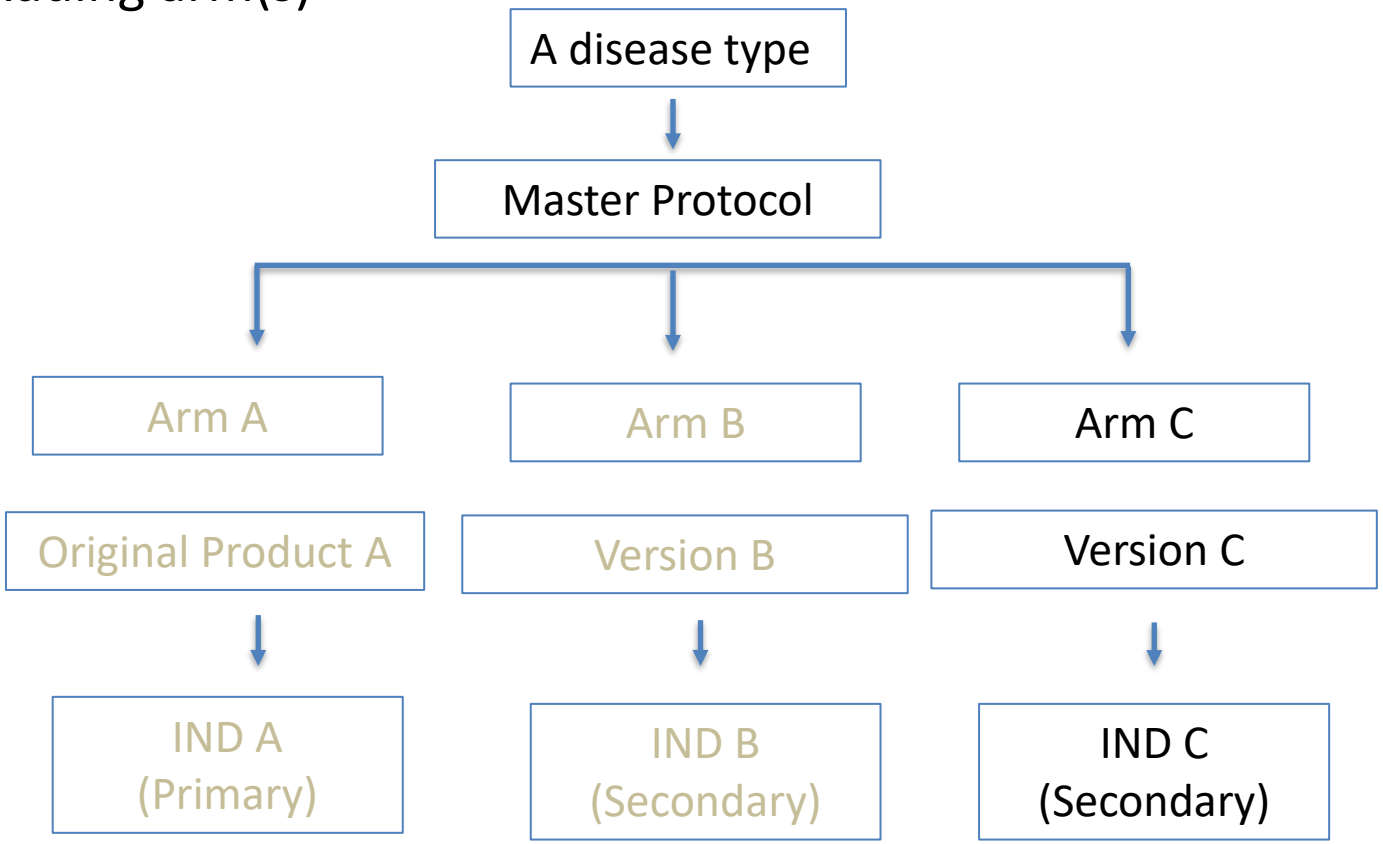
Adding arm(s)



Regulatory implications:

- IND C (new secondary IND) :
  - CMC, P/T modules for IND C
  - Cross-reference clinical information to IND A
- Amendment to IND A (primary IND) containing
  - A revised clinical protocol to include Arm C
  - Revised IB, IC, Form 1572 (if applicable)
  - Cross-reference CMC, PT information to IND C
- No change to IND B

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Potential benefits:

- Less regulatory burden for industry
- Less costly in preparing individual INDs
- Same protocol with same study population allows dropping or adding an arm, and preliminary exploratory comparison for safety and clinical activity
- More efficient clinical operation (not having individual trials for each version of the product)

FDA CBER Guidance Agenda 2021*

Guidance Documents CBER Is Planning to Publish During Calendar Year 2021 for Category of Tissues and Advanced Therapies:

- Considerations for the Development of Human Gene Therapy Products Incorporating Genome Editing; Draft Guidance for Industry
- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Therapies; Draft Guidance for Industry
- Studying Multiple Versions of a Cellular or Gene Therapy Product in a Clinical Trial; Draft Guidance for Industry

* https://www.fda.gov/media/120341/download

Summary

- Master protocol for early CGT trials may be helpful to expedite the clinical development:
  - Context: exploratory, early, dose-finding, activity finding trials, no concurrent control; applicable for studying multiple versions of a CGT under one trial
  - Goal: select candidate(s) (choose winner(s)) for further development with less regulatory burden and more efficiency.
- To be published FDA draft guidance on “Studying Multiple Versions of a Cellular or Gene Therapy Product in a Clinical Trial” will be very helpful.