Innovations for effective drug development
Promoting Effective Drug Development Programs: Opportunities and Priorities for FDA’s Office of New Drugs

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Agenda

› Innovative approaches to accelerate development
› Design options for dose escalation
› Seamless Phase I/II design
› Considerations for more effective drug development
Survey demonstrates impact of innovations - low adoption rates and barriers

**THE INNOVATION IMPERATIVE: THE FUTURE OF DRUG DEVELOPMENT**

<table>
<thead>
<tr>
<th>Innovation Type</th>
<th>Reduction In Enrollment Time</th>
<th>Likelihood of Launch</th>
<th>Adoption rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive Trials</td>
<td>↓ 4.2 Months</td>
<td>13%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Precision Medicine Trials</td>
<td>↓ 5.2 Months (Oncology) ↓ 0.9 Months (Neurology) ↓ 10.6 Months (Rare Diseases)</td>
<td>10%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Patient Centricity</td>
<td>↓ 3 Months</td>
<td>19%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Real-World Data Trials</td>
<td>↓ 1 Month</td>
<td>21%</td>
<td>0.3%</td>
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**Enablers**
- Advanced Data Analytics
- Workforce Readiness
- Collaborative Partnerships
- Early Regulator, Payer, & Patient Involvement

**Barriers for Adoption**
- Vast, New and Fragmented Data
- Small or Inadequate Workforce
- Negative Perceptions of Pharma
- Cultural Barriers

https://druginnovation.eiu.com
Commissioned by Parexel
Dose Escalation Designs used in Oncology

- **Rule based**
  - Simple up and down, 3+3 type, $i3+3$, accelerated titration

- **Model Based**
  - Continual Reassessment Method (CRM) and modifications
  - Escalation with Overdose Control (EWOC)
  - Bayesian Optimal INterval (BOIN) Design
  - Modified toxicity probability interval design (mTPI, mTPI 2)
  - Toxicity and efficacy probability interval (TEPI)

- **Comparison Rule/Model based Trials**

<table>
<thead>
<tr>
<th>N=172 trials*</th>
<th>Rule-based</th>
<th>Model-based</th>
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<tbody>
<tr>
<td>Duration of trials</td>
<td>36 mo</td>
<td>26 mo</td>
</tr>
<tr>
<td># Patients below RP2D</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>Safety: DLTs</td>
<td>14%</td>
<td>13%</td>
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Seamless Phase I/II Study
Combining Dose Escalation and dose expansion

Dose levels: 50, 100, 200, 400, 600 mg QD

Patient selection:
- Cohort A - Melanoma
- Cohort B – NSCLC
- Cohort C – H&N
- Cohort D - Gastric

Simon 2 stage design:
Futility criteria for hypothesis of ORR=5% vs 20%:
- 0/10 after stage 1
- 3/29 after stage 2

Futility criteria for hypothesis of ORR=10% vs 25%:
- 2/18 after stage 1
- 7/43 after stage 2

Stage 1 decision
Stage 2 final analysis

Dose escalation

MTD/RP2D
Synthetic Control Arm
Real World Evidence to Support Development of Drugs and Biologics

Single arm Clinical Study (CS)

RWD collection
- Patient-level data in similar patients

Matching algorithm applied to RWD
- Create a matching cohort to CS cohort

Comparative analysis CS vs RWD cohorts
- Demonstrate superiority of CS treatment vs RWD control cohort

Considerations for more effective drug development

Use more efficient study designs in early development

- Apply innovations – Adaptive trial designs, Precision medicine, Patient centricity, RWD
- Apply model based dose escalation designs and expansion designs to oncology and non-oncology studies
- Consider RWD to support development through synthetic control arms
  - Agree on acceptable methodology
Thank you