Digital Health and Big Data for Drug Development

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Statistical and Computational Challenges in Precision Medicine
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Digital Health and Clinical Trial

- Digital Health: the convergence of digital technologies with healthcare to make healthcare delivery efficient and patient-centric.

[FDA Digital Health Innovation Action Plan 2017]
Scope
- Mobile Health
- Wearable device
- Health IT
- Telehealth & Telemedicine
- Personalized medicine

Utilities
- Reduce inefficiencies and costs
- Improve access & quality
- Make medicine personalized for patients
Video endoscopy

- Background: a drug to control the inflammation of intestine lining is being developed. The team needs to assess the level of inflammation before and after treatment. But endoscopy procedure alone could scare patients away …
• Background: Safety monitoring is a critical part of drug development. Continuous monitoring of heart activities may be required to ensure patient’s safety during some clinical trials.
Digital predictive biomarkers

- Background: AD trial is very challenging, partially because of the low conversion rate from MCI to AD dementia. Can we enrich the patients population to improve trial efficiency?

“ACRs ranged from 7.5 to 16.5% (7 studies, median: 11.0%) per person-year for studies recruiting from clinics, and from 5.4 to 11.5% (7 studies, median: 7.1%) for community samples.”
According to most reviews the mean rate of medical adherence in different psychiatric conditions lies somewhere in the range of 10% to 75%. Non-adherence in clinical trial will mask a potential efficacy signal, as well as safety signal.
Design Considerations
Pilot study to assess feasibility

- wearable ECG devices can generate 10 millions data points per day
- false signals occurs occasionally (~0.1%)

- but it means ~100 false signals to deal with every day!!!
Sample Size

**Compare two group means using post-treatment measurements only**

\[ y_{ijk} = \mu_i + S_{ij} + \epsilon_{ijk} \]

- \( \mu_i \): treatment effect
- \( S_{ij} \): subject effect related to inter-subject variability \( \sigma_B^2 \)
- \( \epsilon_{ijk} \): measurement error related to intra-subject variability

\[
n = \frac{f(\alpha, \beta)}{\Delta^2} \cdot 2 \cdot (\sigma_B^2 + \Sigma^{(*)}) \propto (\sigma_B^2 + \Sigma^{(*)})
\]

**Compare two slopes using longitudinal measurements**

For each subject in each treatment

\[ y_{ijk} = \alpha_{ij} + \beta_{ij} \times k + \epsilon_{ijk} \]

\( \epsilon_{ij} \sim MVN(0, \Sigma^{(*)}) \)

- \( \hat{\beta}_{ij} = \mu_i + S_{ij} + r_{ij} \)
- \( \text{var}(S_{ij}) = \sigma_B^2 \) corresponding to the inter-subject variability
- \( \text{var}(r_{ij}) = \sigma_W^2 \) corresponding to the intra-subject variability due to estimation

\[
n = \frac{f(\alpha, \beta)}{\Delta^2} \cdot 2 \cdot (\sigma_B^2 + \sigma_W^2)
\]
Relative efficiency: digital vs traditional measurements

\[ n \propto (\text{Inter-Subject Variation} + \text{Intra-Subject Variation}) \times \text{Error Variation} \]

- Digital measurements tend to have higher measurement error, but lower intra-subject variation.
- In contrast, traditional measurements tend to have lower measurement error, but higher intra-subject variation.
- The lower intra-subject variation is due to the fact that digital measurements tend to be high frequency in nature, which can be averaged to reduce intra-subject variation.
- But can intra-subject variation be reduced to zero with very high frequent digital measurements?

\[ \bar{\Sigma}^* = \sigma^2 \cdot \frac{1}{D^2} \left( D + 2 \sum_{i=1}^{D-i} iC^{D-i} \right) \cdot \frac{1}{r^2} \left( r + 2 \sum_{j=1}^{r-1} j \rho_{r-j} \right) \]
Applications of Big Data

Text data
• MOA
• Social Listening
• Competitive intelligence

Genomics data
• Joint analysis for novel insights
• Joint analysis to increase power
• Predictive biomarker modeling

External clinical data
• virtual control arm
• Identify novel prognostic factors
• network meta analysis

RWD
• trial simulation
• Identify new endpoints

Digital Health
• digital endoscopy
• wearable device
• digital biomarker
• digital medical assistant
Conclusions

- The promise of precision medicine relies on our ability to collect detailed patient profiles.

- Digital technology can compliment genomics to provide deep phenotype of patients.

- Innovation is DNA of pharma R&D.

- Digital Technology + Big Data + Statisticians together can play critical roles for precision medicine.
Our Aspiration

We use Statistics to innovate R&D and empower data to guide decision making

- Biomarker
- PRO
- RWD
- External data
- Digital data
- Text data
- Discovery
- CMC

Provide information to help project statisticians to design better trials
Takeda History: 237 years and counting

1781
Takeda founded by Chobei Takeda I

1962-1997
Takeda expands its overseas operations into Asia, the US and Europe

2008
Takeda acquires Millennium $8.8 B

2011
Takeda acquires Nycomed $13.7 B

2017
Takeda acquires Ariad $5.2 B

2018
Takeda to acquire Shire $62 B

Internal Confidential
THANK YOU

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