Webinar: Knowledge-based approaches to decreasing clinical attrition rates

Speakers:
Dr. Richard K. Harrison
Gavin Coney
Teresa Fishburne

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• Clarivate Analytics is the global leader in providing trusted insights and analytics to accelerate the pace of innovation

• Delivering intelligence for Life Science professionals in discovery, preclinical, clinical, commercialization and generics

• Powering life science data and trusted content with analytics

• Clarivate Professional Services offer unrivalled data science expertise, evidence-based consulting and independent advice across the pharmaceutical R&D value chain
Clarivate Analytics speakers

Dr. Richard K. Harrison
Chief Scientific Officer

- Over 30 years of experience in the life sciences industry
- Career has focused on all aspects of pre-clinical drug discovery
- Has held positions of increasing responsibility at Aventis, Merck, DuPont and Wyeth Pharmaceuticals

Gavin Coney
Head of Clinical Products

- Supports decision making by professionals within Life Science organizations who are interested in gaining intelligence relating to:
  - Clinical Development
  - Clinical Operations
  - Competitive Intelligence
- Has worked within informatics for 18 years and within the Life Sciences for the last 8 years

Teresa Fishburne
Head of Clinical & Regulatory Professional Services

- Over 20 years of industry experience in Clinical Operations, Regulatory Affairs and Quality management
- Manages a team of clinical and regulatory professionals that create high-value solutions to address customers’ ever-evolving needs for strategic intelligence.
Industry Overview

Dr. Richard K Harrison
What is the current rate of clinical trial attrition?

- According to the Centers for Medical Research (CMR) the probability of success moving from Phase 1 to market is less than 10% over all therapy areas

Ref: CMR Factbook, 2016
What are the main causes of attrition?

- Efficacy is the reason for failure in more than half of Phase II and Phase III trials
- Failure is across all therapy areas with Oncology being the greatest

What are the main causes of attrition?

- According to a study by Astra Zeneca, 40% of their projects failed in clinical trials because no clear link was made between the target and the disease.

- An additional 29% failed because the compound chosen did not have the correct physical properties or did not reach the target tissue.

**Reasons for lack of efficacy**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target linkage to disease not established or no validated models</td>
<td>40 (18)</td>
</tr>
<tr>
<td>available</td>
<td></td>
</tr>
<tr>
<td>Dose limited by compound characteristics or tissue exposure not</td>
<td>29 (13)</td>
</tr>
<tr>
<td>established</td>
<td></td>
</tr>
<tr>
<td>Indication selected does not fit strongest preclinical evidence</td>
<td>20 (9)</td>
</tr>
<tr>
<td>Evidence from previous phase not robust enough</td>
<td>11 (5)</td>
</tr>
</tbody>
</table>

Percentage for all reported reasons (total number of projects: 28)

Nature Reviews Drug Discovery 13
419-431 (2014)
Clinical failure rates and reasons for failure

- According to the Centers for Medical Research (CMR) in the year 2015 the probability of success moving from Phase 1 to market is less than 10% over all therapy areas.

- Efficacy is the reason for failure in more than half of Phase II and Phase III trials.

- According to a study by Astra Zeneca 40% of their projects failed in clinical trials because no clear link was made between the target and the disease.
  - An additional 29% failed because the compound chosen did not have the correct physical properties or did not reach the target tissue.
Knowledge based approaches to decrease attrition

- Insights into trial endpoint success
  - Increased use of biomarkers to decrease attrition
  - Correlation to trial success
  - Optimum number of biomarkers

- The impact of protocol amendments on trial success
  - Impact budget planning,
  - Impact on patient enrollment
  - Impact on cycle times.

- Incorporating strategies to reduce the number of amendments
  - When are amendments required
  - Making amendments more effective.

Source: Clarivate Analytics, Cortellis Clinical Trials Intelligence
Insights Into Trial Endpoint Success

Gavin Coney
Trial protocol design: rising data / intelligence challenge

Granularity of disease understanding: more datapoints and greater specificity

Advances in Personalized Medicine Improve Outlook for Patients with Blood Cancers

A greater understanding of the molecular basis of disease has transformed what was once known collectively as “disease of the blood” into multiple subtypes of leukemia and lymphomas with a 5-year survival rate of 70% collectively.

Increasing data collection (Datapoints collected per patient visit)

Rising volumes of published results

Real World Evidence

Increased data volumes from multiple cohorts

Digital Health

Cap Gemini, Healthcare survey
### Dataset: Granular trial design components indexed for every trial

<table>
<thead>
<tr>
<th>Trial / Intervention</th>
<th>Trial milestones</th>
<th>Trial Protocol Insights</th>
<th>Patient Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Condition</td>
<td>• Start Date</td>
<td>• Patient Segment</td>
<td>• Sponsor / Collaborator</td>
</tr>
<tr>
<td>• Phase</td>
<td>• Primary Endpoint</td>
<td>• Biomarker</td>
<td>• Commercially Relevant?</td>
</tr>
<tr>
<td>• Recruitment Status</td>
<td>Completion Date</td>
<td>• Biomarker Type</td>
<td>• Site Name</td>
</tr>
<tr>
<td>• Interventions</td>
<td>• Enrolment End Date</td>
<td>• Biomarker Role</td>
<td>• Contact Name</td>
</tr>
<tr>
<td>• Combination?</td>
<td>• End Date</td>
<td>• Age</td>
<td>• City</td>
</tr>
<tr>
<td>• Action</td>
<td></td>
<td>• Race</td>
<td>• State</td>
</tr>
<tr>
<td>• Class</td>
<td></td>
<td>• Inclusion Criteria</td>
<td>• Country</td>
</tr>
<tr>
<td>• Intervention Category</td>
<td></td>
<td>• Exclusion Criteria</td>
<td>• Region</td>
</tr>
<tr>
<td>• Trial Design</td>
<td></td>
<td>• Endpoints</td>
<td>• Enrolment Count</td>
</tr>
<tr>
<td>• Active Control</td>
<td></td>
<td>• Endpoint Types</td>
<td>• Enrolment Rate</td>
</tr>
</tbody>
</table>

- Over 300,000 Trials
- Focus on drugs, biomarkers and devices
- All therapy areas; Global coverage

**Source:** Cortellis Clinical Trials Intelligence, Clarivate Analytics, April 2018
Rising use of biomarkers

| Disease marker: The biomarker indicates if a disease already exists (diagnostic biomarker), or how such a disease may develop in an individual case regardless of the type of treatment (prognostic biomarker). |
| Therapeutic effect marker: The biomarker gives an indication of the probable effect of treatment on the patient |
| Toxic effect marker: The biomarker indicates a treatment-related adverse reaction |

Coney, Gavin. Clarivate Analytics, Cortellis Clinical Trials Intelligence. www.clarivate.com
Growth in trial volume by phase

All trials within the time period, irrespective of whether the trial endpoints were met

Source: Cortellis Clinical Trials Intelligence, March 2018
Trial endpoint success: Reporting bias

- Phase 1 – 4
- 4,550 trials with known outcomes with start date 2005 or later
- Trial endpoint success determined by explicit statement made by sponsor referencing the endpoint

Source: Cortellis Clinical Trials Intelligence, March 2018
Are phase II trials failing quietly? Focus on phase 3 successes

Commercially Relevant: Is the primary intervention being studied owned by the trial sponsor?

Source: Cortellis Clinical Trials Intelligence, March 2018
Biomarkers and trial endpoint success

<table>
<thead>
<tr>
<th>Are Biomarkers Used?</th>
<th>Proportion Of Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>21.3%</td>
</tr>
<tr>
<td>No</td>
<td>78.7%</td>
</tr>
<tr>
<td>Yes</td>
<td>27.8%</td>
</tr>
<tr>
<td>No</td>
<td>72.2%</td>
</tr>
</tbody>
</table>

Is at least one biomarker applied within the trial design. Could be biomarker for efficacy, toxicity or disease

Source: Cortellis Clinical Trials Intelligence, March 2018
Number of biomarkers vs endpoint success by phase

- All trials with known outcome; Segmented By Phase and then trial endpoint status
- Mean of Number of Biomarkers within each of the 8 groups

Source: Cortellis Clinical Trials Intelligence, March 2018
Segmenting biomarker role and endpoint success

- All trials categorized according to the combination of biomarkers
- Ranked by descending number of trials that were reported to have reached their endpoint (green = yes; red = no)
- Yellow bar displays the % of trials in each category that were reported as successful

Source: Clarivate Analytics, Cortellis Clinical Trials Intelligence
Endpoint success and application of biomarker roles

Rank order now selected as % of trials in category that were reported as reaching their endpoint

Source: Clarivate Analytics, Cortellis Clinical Trials Intelligence
Summary

- A biomarker strategy has been seen to positively impact likelihood of meeting trial endpoint
- That effect is not uniform:
  - Positive Phase 2-4; Negative Phase 1
  - Toxic Effect markers strongly associated
  - Disease markers not strongly correlated
- Need for the best intelligence to inform protocol design
Impact and Strategies Relating To Trial Amendments

Teresa Fishburne
Amendments

Source: CMR Global Clinical Performance Metrics Programme. CMR International, a Clarivate Analytics business

Source: Getz, et al Tufts CSDD
Budget impact and key facts

- $20 Billion annual spend in direct and indirect costs
- 45% of all amendments are avoidable
- 2/3 Phase III trials > 1 global amendment
- 74% of all Phase II trials > 1 global amendment
- Rare diseases amendments > non-rare

Source: CMR Global Clinical Performance Metrics Programme. CMR International, a Clarivate Analytics business
Source: Getz, et al Tufts CSDD
Enrollment and cycle times

Data are shown for Phase I, Phase II and Phase III studies that completed enrolment (Last Patient Enrolled milestone) between 2011 and 2015 and had one or more protocol amendment. This analysis includes ongoing and terminated studies.

Strategies

❖ Biomarkers
❖ Inclusion / Exclusion Criteria

Source: CMR Global Clinical Performance Metrics Programme. CMR International, a Clarivate Analytics business
Source: Getz, et al Tufts CSDD
Strategy to reduce amendments – use of biomarkers

- Rare disease programs and programs that utilized selection biomarkers had higher success rates at each phase of development vs. the overall dataset.
- A three-fold higher likelihood of approval from Phase 1 was calculated for programs that utilized selection biomarkers (25.9%, n=512) vs. programs that did not (8.4%, n=9,012).
- Bio article concluded that the enrichment of patient enrollment at the molecular level is a more successful strategy than heterogeneous enrollment.
- ~150 biomarkers are included on FDA approved drug labels. Such a strategy is associated with improved approval success and reduced approval timelines.

Source: Clarivate Analytics, Cortellis Clinical Trials Intelligence
Source: Hay et al; Clinical development success rates for investigational drugs. Nature Biotechnology (2014)
Source: BIO, Biomedtracker (2016)
Strategy to reduce amendments – Inclusion/exclusion criteria

- Newly emerging medical knowledge
- Regular violations of entry criteria
- Low recruitment rates

- Build off approved/launched competing drugs with like MOA/indications
- Build off internal Phase 1/2
- Literature search
  - New or novel criteria
- Incorporating Biomarkers:
  - By roles (Therapeutic effect, disease marker, toxic effect)
  - By type (genomic, proteomic, physiological, biochemical, cellular, structural, anthropomorphic)
- Biomarkers to address responders vs non-responders

Source: Clarivate Analytics, Cortellis Clinical Trials Intelligence
## Overall strategy to reduce amendments – Key points

### Protocol Review
- 19 additional days of internal review = 0 or 1 amendments
- Longer internal review time = shorter trials
- Incorporate more internal review approaches
- Bundle non-urgent amendments, where applicable

### Biomarkers
- Programs that utilized selection biomarkers had higher success rates at each phase of development vs. the overall dataset.
- Enrollment at the molecular level is a more successful strategy than heterogeneous enrollment.
- ~150 biomarkers are included on FDA approved drug labels.

### Inclusion / Exclusion Criteria
- Using internal data to build criteria
- Build off approved/launched competing drugs with like MOA/indications
- Assess feasibility / appropriateness
- Use of predictive biomarkers to identify responders vs non-responders
Questions

Cortellis images, CTI, CCI

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