SynteractHCR

What makes clinical trials in orphan indications so special?

3 MARCH 2014

Milestone Legislations

§§

- 1983: US Orphan Drug Act
- 2000: EU Parliament and Council Regulation EC 141/2000
- 2000: EU Commission Regulation 847/2000
- 2002: US Rare Diseases Act

Costs vs. Disease Frequency

$$

- A self-healing, short, temporary, harmless disease would not justify high costs of a therapy.
- The potential of a disease to create sequelae (lasting damages) or reduce life expectancy is a decisive factor to justify high costs for development of new therapies and for the market price of new drugs.
- In a rare disease, the costs for development of a new therapy will be seen in relation to a very small number of individual patients. The price per prescription may become astronomical.

➔ Public incentives and facilitations make drug development for rare diseases more financially viable.

➔ Significant increase in clinical trials in orphan indications

What is 'rare'? – What is 'orphan'?

Definition of Rare Disease

- Depends on the frequency of a disease in the general, total population.
  - "Rare" means "less than 1 patient per *xxx* people."

- Definition is arbitrary. Authorities in different countries or regions use different cut-off values:
  - In USA: < 1/1500
  - In EU: < 1/2000

Definition of Orphan Disease

- A disease "forgotten" by treatment
- A disease for which there is no treatment
- There may be measures available to attenuate the symptoms or risks for complications, but there is nothing to change (prolong) the natural course of the disease or the damage caused by the disease.

Note: In colloquial language, the word "orphan" is sometimes used also to denote a medicine – *"an orphan drug for an orphan disease".*

Orphan & Rare

A disease can be ...

- ... rare, but not orphan, if there is an effective treatment.
- ... frequent and orphan, if there is no effective treatment.

USA Orphan Drug Act defines:

An orphan drug is a drug for a rare disease for which there are no adequate drugs available.

- **Orphan** drug treatment of a **rare** disease

Unique characteristics of clinical trials in rare diseases

Chronic-Deteriorating Disease

- The disease creates damages with secondary conditions and symptoms, which need additional treatments

➔ Complex Case Report Forms

- Patients are scattered across the country. Even a big medical center has only relatively few patients.

➔ High number of study sites

- Incidence (newly diagnosed patients) is extremely low. A study must rely on patients who are already known.

➔ Pro-active recruitment efforts

Scientific Limitations

$E = mc^2$

- Due to the rarity, a statistically powerful study with a high sample size may not be feasible. "Statistical significance" may be limited.
- Two studies (as otherwise typical) may not be feasible, because the existing patients may hardly be sufficient to fill one study.
- True surrogate variables may not exist; accepted biomarkers may be available, but not truely validated as prognostic factors or disease course indicators.

➔ Analysis of individual patients and comparison with historic data can be acceptable.

Strategy with Authorities

- Case-by-case decision of authorities, which facilitations (deviations from scientific "gold standard") are acceptable

- Drug (product) development path to marketing authorisation is highly individualised.

➔ Clinical drug development should always be done based on extensive, thorough pre-IND (in USA) or Scientific Advice (in EU) by authorities.

Unique characteristics of clinical trials with orphan treatments

Use of Placebo

?!

- When there is no treatment and the safe investigational drug is the only (even if only theoretical) hope
  – how can we justify not giving it?
  - ➔ After a placebo-controlled, double-blind study, non-responder patients are offered the investigational product as open-label extension; this also creates additional safety data.

- When the disease will inevitably create damage
  – how can we justify withdrawing concurrent treatment in order to have a "clean" placebo-controlled study?
  - ➔ Investigational product is add-on to baseline care
  - ➔ Open-label extension study with new drug for all
  - ➔ Cross-over design where everyone gets the new drug at least once; only in selected situations, difficult for biostatistical analysis and for correct interpretation of results

High Motivation of Patients

- People who learn that they have "something special" are pro-actively looking for information.
- As there is no convincingly effective treatment, patients tend to seek for help pro-actively; informal and formal interest groups are often formed.
- Patients are willing to try something new, provided that it is sound and serious.
- Patients are keen to be in a study and willing to take a more-than-average burden imposed by the study.

Compliant Patients

- Compliant patients have learnt to live with their disease.
- They know that the doctor can not do much about it.
- Stabilized, well-managed patients see no reason for frequent doctor visits, unless there is something acute.

➔ A "*Sit and wait until someone comes*" recruitment strategy for a clinical trial is bound to fail.

Patient Recruitment Strategy: Pro-active Visibility

- Database search at study sites
- Contact interest / self-aid groups and internet forums
- Presentation at medical congresses; some doctors may tell their patient(s) about the study or may even want to participate in the study
- Create study website, with search-engine optimisation
- Advertisement in suitable media; even if patients don't see it, a friend or relative may see it and inform the patient

SynteractHCR experience in rare diseases

SynteractHCR Approach
(data status 15 Feb 2014)

- 94 clinical trials in rare diseases, in
- 30+ different rare diagnoses
- Feasibility group looks globally at
  - Incidence
  - Prevalence
  - Patient management
  - Treatment landscape
  - Competing studies
  - Scientific attractiveness of the new therapy
  - Logistical attractiveness of the new trial
  - Interest among potential study sites

➔ Integrated assessment of project feasibility

SynteractHCR Indications - Examples

- Ataxia teleangiectatica
- Behcet's disease
- Hemophilia
- Hereditary angioedema
- Hereditary chronic cholestasis
- Cystic fibrosis
- Duchenne muscular dystrophy
- Gaucher's disease
- Gliobastoma multiforma
- Growth hormone deficiency
- Hepatic fibrosis
- Hodgkin's disease
- Idiopathic pulmonary fibrosis
- Idiopathic thrombocythemia
- Idiopathic thrombocythopenia
- Insulin-like growth factor 1 deficiency
- Lupus erythematodes
- Lymphocytic leukemia
- Myeloma
- Myelodysplasia
- Pemphigus vulgaris
- Precocious puberty
- Sarcoidosis
- Scleroderma
- Urea metabolism disorder

Dr. Stephan de la Motte
Chief Medical Advisor

www.SynteractHCR.com

Corporate Headquarters

5759 Fleet Street, Suite 100
Carlsbad, CA 92008

Tel: +1 760 268 8200

International Locations

Argentina
Austria
Belgium
Czech Republic
Denmark
France
Germany
Israel
Italy
Poland
Russia
Spain
Sweden
Ukraine
United Kingdom
USA

www.SynteractHCR.com