La recherche clinique et l’innovation à l’hôpital en 2018
Enjeux et pratiques

EHESP Rennes

Les fondamentaux de la recherche clinique

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Agenda

- Objectives: product-centred vs. patient-centred trials
- Trial design and methodology
- Regulated research: regulation, ethics, data protection
- Multinational cooperation to address health challenges
- Costs and funding
- The digital revolution
Objectives of clinical research
The other was the best recovered in his condition; and being now pretty well, was appointed nurse to the rest of the sick. Next to oranges, I thought the cyder had the best effects.

- James Lind -
Need for clinical trials

- 1 - Development of innovative health products
  - registration trials
  - phase I – II – III

- 2 - Repurposing trials
  - exploring new indications for authorised products
  - phase II – III

- 3 - Comparative efficacy/ safety / effectiveness trials
  - compare efficacy and safety of authorised healthcare strategies
  - phase IV

Risk categories

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New product
Modified use
Usual care
Product centred vs. patient centred research

Registration trials vs. Repurposing trials

- Comparative effectiveness
  - mostly academic
- Personalized medicine
  - mostly industry
Sponsor, investigator, patients
Distribution of roles in multinational trials: trial management vs. investigation

Investigator- or SME-initiated trial

- Sponsor
- CTU
- ECRIN
- PI

Industry-sponsored trial

- Sponsor
- CTU
- ECRIN
- +/- CRO

Trial management

Investigation
Trial design and methodology
Levels of scientific evidence

Interventional (causality)

Observational (correlation)
Stages of clinical development

Preclinical

Laboratory Studies

Human Safety

Phase I

Efficacy & Safety

Phase II

Comparing standard treatment

Phase III

Post Approval

Phase IV
Overview of clinical development

- 10K compounds
- High attrition rate
- 1 drug to market

- Preclinical Phase incl. Research
- Clinical Phase I
- Clinical Phase II
- Clinical Phase III
- Registration

- Safety / PK
- Proof of concept / Dose finding
- Efficacy

- Development

~ 11-15 years
Phase I study

- **Single ascending dose (SAD)**
  - healthy (male) volunteers
  - each cohort n=8, 6 active and 2 placebo, blinded, randomised
  - dose escalation (can be stopped at any time)
  - up to MTD (max. tolerated dose, based on number of AEs)
  - PK / PD secondary objective

- **Multiple ascending dose (MAD)**
  - once single dose MTD established
  - cohort n=8, 6 active and 2 placebo, blinded, randomised
  - eg. one dose daily for 10 days
  - evaluate safety and tolerability at steady state
Single ascending dose

Stopping rule based on number of SAEs -> MTD ?
Stop

Cohort (8 subjects, 6 active, 2 placebo)

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PK : one-compartment model

Dose

Stomach
concentration in stomach = $C_1(t)$

Blood
absorption rate=$k_a$
concentration in blood = $C_2(t)$
excretion rate=$k_e$

$C_2(t) = \frac{F \times D \times k_a}{V(k_a - k_e)} \left( e^{-k_e t} - e^{-k_a t} \right)$

$D =$ Dose 
$t =$ time 
$F =$ Fraction absorbed (bioavailability) 
$V =$ Volume of distribution 
$k_a =$ absorption rate 
$k_e =$ elimination rate
Multiple ascending dose

- MAD - Dose Level 1
- MAD - Dose Level 2
- MAD - Dose Level 3
- MAD - Dose Level 4
- MAD - Dose Level 5

E.g., one dose taken daily for 10 days 6:2 (active:placebo) randomization
Multiple ascending dose
Phase IIa trials: proof of concept

- Relevance AND significance? -> GO or STOP
  - typically randomized assessment of efficacy
  - statistical significance AND clinical relevance
  - Bayesian methodology suitable
  - clinical relevance / amplitude of effect: define target clinically relevant difference / placebo (usually lower than effect of reference treatment)
  - and statistical significance vs. placebo (\( \alpha = 10\% \) 1-sided)

| \( \Pr(\theta > 0 | \text{data}) \) | \( \Pr(\theta > 0 | \text{data}) \geq 0.90 \) | \( \Pr(\theta > 0 | \text{data}) < 0.90 \) |
|----------------------------------|---------------------------------|---------------------------------|
| \( \Pr(\theta > 5 | \text{data}) \) \(|\) | \( \Pr(\theta > 5 | \text{data}) \geq 0.50 \) | \( \Pr(\theta > 5 | \text{data}) < 0.50 \) |
| relevance                       | GO                              | INDETERMINATE                   |
|                                 |                                | STOP                            |
Phase IIb trials: dose finding

- determine dose-response relationship
  3 to 4 doses if curve known (Scatchard-like model)
  1 – 2 – 4 – 8

- what is the effect size?
- what is the smallest dose with (almost) maximal effect?
- which doses lead to an unacceptable efficacy / safety?
  (therapeutic window?)
- choose the dose for the phase III
Dose finding: dose-response relationship

All things are poison and nothing is without poison, only the dose permits something not to be poison.

- Paracelsus (1493-1541)
Dose finding: dose-response relationship

Response = \( E_0 + E_{\text{max}} \frac{D^h}{ED_{50}^h + D^h} \)

- \( E_0 \): Baseline response
- \( E_{\text{max}} \): Maximum response
- \( ED_{50} \): Half maximal effective dose
- \( D \): Dose
- \( h \): Parameter indicating the steepness of the response curve
# Overview of clinical development

<table>
<thead>
<tr>
<th>Phase</th>
<th>Sample size per study</th>
<th>Length per study</th>
<th>Study population</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>I First in human/PK</td>
<td>6 – 20</td>
<td>Weeks – Months</td>
<td>Healthy volunteers</td>
<td>Safety, pharmacokinetics &amp; pharmacodynamics; determining maximum tolerated dose (MTD)</td>
</tr>
<tr>
<td>II First in patients</td>
<td>50 – 200</td>
<td>Months</td>
<td>Patients</td>
<td>Proof of concept; dose finding</td>
</tr>
<tr>
<td>III Submission</td>
<td>200 – 10,000</td>
<td>Months – Years</td>
<td>Patients</td>
<td>Confirmatory</td>
</tr>
<tr>
<td>IV Post approval</td>
<td>Broad range</td>
<td>Broad range</td>
<td>Patients</td>
<td>Post marketing Health Authority commitments; health economics; pharmacovigilance</td>
</tr>
</tbody>
</table>
Clinical trial design and methodology

- Clinical trials:
  - prospective experiment
  - compare randomised groups
  - no confounding factor, causality

- Ideally: randomised, double-blind, controlled

- Controls
  - placebo
  - active comparator
  - uncontrolled? placebo effect, regression to the mean
  - historical control? patient, treatment, evaluation may differ
  - ideally concurrent: same time period

- Randomisation
  - simple (unbalanced?) (ex. ABAAABABABAAABABAABBB...)
  - blocked (predictability?) (ex. ABBA ABAB BBAA BAAB....)
  - stratified (balance sex, age)
Outcome measures and blinding

- **Outcome measures**
  - standardized, patient-relevant, avoid surrogate endpoints
  - statistical power calculated for primary endpoint

- **Blinding : avoid bias**
  - double blind : patients and investigators
  - single blind
  - open
  - blinded independent review

- Similar treatments, or double-dummy

- Surgery trials : sham ?
- Psychotherapy, physiotherapy ?
  - make assessors blind
Parallel groups vs. cross-over design

- **Parallel groups**
  - patients assigned to one group

- **Crossover trials**
  - fewer patients, test “within” (not “between”) patients
  - washout
  - not if carry-over effect
  - not for curable diseases or long-term treatments
  - patients stay for a longer time period in trial
Superiority, non-inferiority, equivalence

- **Design:** based on question
  - new drug > placebo
  - new drug + standard > standard
  - new drug > or = to standard
Insensitive non-inferiority trial

true effect new treatment vs comparator

reduced effect due to
- “sloppy” measurement
- wrong time point
- insensitive analysis, etc.

$H_0$

Non-inferiority
Statistical considerations in clinical trials

- **Statistical analysis plan pre-specified (and registered)**
  - sample size calculation based on primary endpoint
  - avoid multiple tests and post-hoc analysis
  - adjustment for multiplicity: Bonferroni, Hochberg

- **Sample size calculation**
  - more patients -> more chance to detect effect (if any)
  - large effect -> small sample size

Based on

\[
n = 2 \left( Z_\alpha + Z [1-\beta] \right)^2 \times \frac{SD^2}{d^2}
\]

- amplitude of effect d (advantage of clinical interest)
- estimated variance SD^2 (good design reduces variability)
- desired power (type-II error, producer’s risk, 1-\(\beta\) = 80-90%)
- required significance level (type-I, consumer’s risk, \(\alpha = 5\%\))

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Regulated research: competent authorities, ethics committees, insurance, data protection
European regulatory context for clinical trials

European Regulations
- Clinical Trial Regulation 536/2014
- Medical Device Regulation 737/2017
- General Data Protection Regulation 2016/679

European Directives
- Directives 2001/20/EC (Main)
- 2005/28/EC (GCP, Monitoring)
- 2001/83/EC
- 95/46/CE and 2002/58/EC (Data protection)
- 2003/94/CE (Manufacturing and authorization)

European Member States National Laws

Competent Authority Rules
- ICH GCP
- FDA / EMA rules

Ethical guidelines
- Declaration of Helsinki

Quality System set up by each sponsor
European legislation on clinical trials: 2001/20/EC
Directive for clinical trials on medicinal products
### National Regulatory Requirements

#### EC
- AT
- DK
- FR
- DE
- HU
- IE
- IT
- ES
- SE
- UK

#### CA
- AT
- DK
- FR
- DE
- HU
- IE
- IT
- ES
- SE
- UK

#### Sponsor
- AT
- DK
- FR
- DE
- HU
- IE
- IT
- ES
- SE
- UK

#### Insurance
- AT
- DK
- FR
- DE
- HU
- IE
- IT
- ES
- SE
- UK

#### AER
- AT
- DK
- FR
- DE
- HU
- IE
- IT
- ES
- SE
- UK

#### Requirements Overview

1. **CT on MP**
   - Phase 1
   - Phase 2
   - Phase 3
   - Phase 4
   - Tissue eng
   - Cell therapy
   - Gene therapy
   - Blood-derived
   - MAb, prot, pept
   - Oligonucleotides
   - Vaccines
   - Fixed combination
   - Multimodal

2. **CT on MDevice**
   - Authorized
   - Non-authorized
   - Authorized
   - Non-authorized

3. **Other TTT Trials**
   - Radiotherapy
   - Surgery
   - Transplantation
   - Transfusion
   - Physical therapy
   - Psychotherapy

4. **Diagnostic Studies**
   - In vivo
   - In vitro
   - Imaging

5. **Nutrition**
   - Nutritional
   - Nutr. Supplements

6. **Other Clin. Research**
   - CAM
   - Biobanks
   - Physiology
   - Pathophysiology
   - Psychology

7. **Epidemiology**
   - Pharmacoepidemiology
   - Interventional
   - Non-interventional
   - Epidemiology
   - Interventional
   - Non-interventional
   - Registries of patients

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**Note:** The table above outlines the national regulatory requirements across different categories such as EC, CA, Sponsor, Insurance, and AER, with specific details on various trials and research studies.
EU clinical trial Regulation 536/2014
Major changes under Clinical Trial Regulation 536/2014

- Regulation, NOT a Directive
- Risk-based approach of clinical trials
- Single application dossier via a EU portal with tacit approval if no response within 60 days
- Transparency of clinical trial results
- New rules on informed consent of subjects
- Introduce the concept of co-sponsorship
- Simplified safety reporting system
2017/745 medical device Regulation

Clinical investigation (1)

- Access to market based on **CE** closer to FDA approval
- Provided by notified bodies, expert groups
- Clinical « investigation » required for implantable class III, and active class IIb delivering drugs
- Objective: assess safety and performance (efficacy ?)
- No guidance on level of evidence, « robustness of data »
- Possible scientific advice / expert groups
- Single sponsor in the EU (or legal representative)
- Provisions for vulnerable populations
2017/745 medical device Regulation

Clinical investigation (2)

- Coordinated clinical trial autorisation / rapporteur country (voluntary until May 2027), opt-out, timelines (45 + 50)
- No coordination for ethical review
- Compliance with ISO 14155:2011 and with Declaration of Helsinki
- Insurance / indemnification (national rules)
- Registration, interoperable / EUdraCT, reporting, lay summary
- Single electronic portal
- Central adverse event reporting system
- EUDAMED database, MD identifier (IUD) : transparency, traceability
- After CE label : repurposing -> autorisation, if not -> notification
RGPD : de la pseudonymisation à l’anonymisation

Liste de correspondance (centre)

<table>
<thead>
<tr>
<th>N°</th>
<th>Nom</th>
<th>Prénom</th>
<th>DDN</th>
<th>Sexe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dupont</td>
<td>Gérard</td>
<td>15/09/1987</td>
<td>M</td>
</tr>
<tr>
<td>2</td>
<td>Dupond</td>
<td>Albert</td>
<td>18/02/1954</td>
<td>M</td>
</tr>
<tr>
<td>3</td>
<td>Durant</td>
<td>Marcelle</td>
<td>24/02/1968</td>
<td>F</td>
</tr>
</tbody>
</table>

Base de données (promoteur)

<table>
<thead>
<tr>
<th>N°</th>
<th>Initiales</th>
<th>DDN</th>
<th>Sexe</th>
<th>Date d'admission</th>
<th>Date de chirurgie</th>
<th>Motif</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DG</td>
<td>sept-87</td>
<td>M</td>
<td>15/03/2017</td>
<td>18/03/2017</td>
<td>cancer</td>
</tr>
<tr>
<td>2</td>
<td>DA</td>
<td>févr-54</td>
<td>M</td>
<td>18/04/2017</td>
<td>19/04/2017</td>
<td>hanche</td>
</tr>
<tr>
<td>3</td>
<td>DM</td>
<td>févr-68</td>
<td>F</td>
<td>19/04/2017</td>
<td>22/04/2017</td>
<td>hanche</td>
</tr>
</tbody>
</table>

Données "anonymes"

<table>
<thead>
<tr>
<th>age à la chirurgie</th>
<th>sexe</th>
<th>Décalage admission</th>
<th>Motif</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>M</td>
<td>3</td>
<td>cancer</td>
</tr>
<tr>
<td>63</td>
<td>M</td>
<td>1</td>
<td>hanche</td>
</tr>
<tr>
<td>49</td>
<td>F</td>
<td>3</td>
<td>hanche</td>
</tr>
</tbody>
</table>
## Méthodologies de référence de la CNIL

<table>
<thead>
<tr>
<th>Types de recherche</th>
<th>Recherche impliquant la personne humaine (RIPH)</th>
<th>Recherche n’impliquant pas la personne humaine, étude ou évaluation en santé (RNIPH)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avis CPP dans tous les cas</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Catégorie 1°</th>
<th>Catégorie 2°</th>
<th>Catégorie 3°</th>
<th>Recherche organisée et pratiquée sur la personne hors finalités RIPH</th>
<th>Recherche sur des données ou échantillons collectés dans un autre cadre (réutilisation de données)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recherches interventionnelles</td>
<td>Recherches interventionnelles à risques et contraintes minimes</td>
<td>Recherche non interventionnelle</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Champ d’application des MR

<table>
<thead>
<tr>
<th>MR-001</th>
<th>MR-003</th>
<th>MR-004</th>
</tr>
</thead>
<tbody>
<tr>
<td>(consentement écrit ou exprès requis)</td>
<td>(information et non-opposition)</td>
<td>(information et non opposition – aménagements information individuelle)</td>
</tr>
</tbody>
</table>

* Pas d’avis CEREES.

### En cas de non-conformité avec les MR*

| Avis CPP + autorisation CNIL (+ saisine INDS possible sur intérêt public) | INDS (secrétariat unique + intérêt public) + avis CEREES + autorisation CNIL (+ saisine INDS possible sur intérêt public) |

* Notamment sur les aspects suivants : information de la personne, nature des données traitées, destinataires des données directement ou indirectement identifiables, risque résiduel élevé etc.
Accès aux données du SNDS

Données de l’assurance maladie
Données des hôpitaux
Causes de décès
Données du handicap
Échantillon des données des complémentaires

SNDS

Extracts à façon
Échantillons généralistes
Données agrégées

Alimentation du SNDS
Mise à disposition des données
Need for multinational cooperation to address global health challenges
Product centred vs. patient centred research

Registration trials  Comparative effectiveness
Repurposing trials  Personalized medicine

mostly industry  mostly academic
International cooperation: industry-sponsored vs. academic trials

International cooperation: industry-sponsored vs. academic trials

Atal et al. “A mapping of 115,000 randomized trials revealed a mismatch between research effort and health needs in none high-income regions J Clin Epi 2018  https://doi.org/10.1016/j.jclinepi.2018.01.006
ECRIN: supporting multinational clinical trials

Operational services

- Access to patients and to medical expertise
- Unlock scientific potential

Development of tools and procedures

- Promote quality, harmonisation, interoperability
- Share tools and procedures
International cooperation

OECD Recommendation on the Governance of Clinical Trials

Facilitating International Cooperation in Non-Commercial Clinical Trials
OCTOBER 2011
Experience of ECRIN data center certification, and perspectives

Raising standards in clinical research — The impact of the ECRIN data centre certification programme, 2011–2016

C. Ohmann a, *, S. Canham b, J. Demotes c, G. Chêne d, J. Lauritsen e, H. Martins f, R.V. Mendes g, E.B. Nicolis h, A. Svobodnik i, F. Torres j

https://authors.elsevier.com/sd/article/S2451865416300825
Cost and funding
Funding for multinational trials
The digital revolution
The digitised clinical trial

- Protocol design
- Site selection
  - patients?
  - investigator?
- Patient selection
- Informed consent
- Data from cohorts / registries
- Electronic health records
- Electronic data capture
- Data from national databases
- Data sharing for meta-analyses, re-analyses, secondary use

- Data reuse
- High-throughput –omics
- Imaging data
- Patient stratification studies
- Multimodal data management

ECRIN

European Clinical Research Infrastructure Network

CLINICAL TRIAL DATA SHARING

BMJ Open
Sharing and reuse of individual participant data from clinical trials: principles and recommendations

- data protection, GDPR
- informed consent
- anonymized / pseudonymized
- access (open vs. controlled)
- standard data format
- security
- type of repositories

Ohmann et al., BMJ Open 2017;7:e018647
http://bmjopen.bmj.com/cgi/content/full/bmjopen-2017-018647?ijkey=79SivGTA9igpfbN&keytype=ref
Thank you!
Any questions?