Payment to subjects in CTs: general overview

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Agenda

- **Reason for an interest in the subject**
- **Results of some exploratory research**
  performed by Yana Maris
  as thesis for her Master in Drug Development
  at the Faculty of Pharmaceutical Sciences of KU Leuven
- **Discussion of the findings**
- **Proposal for a way forward**
- **Your thoughts, experience and opinions**

Our research project: *objectives* and methodology

The project consisted of 3 parts:

- ***What is already known about the subject?***
  - ▸ **Thorough literature review**
- ***What is the current practice in Belgium?***
  - ▸ **Analysis of 231 clinical trials evaluated by the REC UZ/KU Leuven during 1 year**
- ***What is the experience and opinion of the different stakeholders involved?***
  - ▸ **Semi-structured interview of 36 reps of 11 different stakeholder groups**

What did we find in the scientific literature and on internet?

82 scientific publications (79 % from USA)

51 gray documents (not exhaustive)

Reasons and forms of compensation/payment

- **Principal reasons:**
  - **Reimbursement of study-related expenses e.g. travel, parking, meal, lodging costs, babysitting**
  - **Compensation for time investment, loss of income, effort, inconvenience, burden**
  - **Incentive or inducement to participate or to complete the trial**
  - **As token of appreciation**

- **Principal forms:**
  - **Financial or monetary: e.g. bank transfer, cash payment, gift certificate or voucher, movie or entertainment park ticket**
  - **In kind: e.g. book, goody bag, toy**
  - **Other forms of compensation: e.g. prospect of therapeutic benefit, earlier and extended access to new treatments, extra investigations or tests, course credits for students, training advice, health counselling, post-study access to free health care,…**

Models of compensation/payment of research participants

Model	Payment serves as	Amount determined by	Potential advantages	Potential disadvantages
Market	Incentive	Supply and demand; market rates	(a) More rapid recruitment. (b) Completion bonuses encourage subject retention and high completion rate. (c) Possibility of profit for participants. (d) Little or no financial sacrifice by subject.	(a) Undue inducement possibly resulting in: incomplete assessment of risks and benefits by subject; subject concealing information to ensure enrollment/retention. (b) Competition between studies; better-funded studies more likely to meet recruitment goals. (c) Different levels of payment at different locations for multicenter trials.
Wage-payment	Compensation	Standardized "wage" for time and effort, suggested to be commensurate with wages for unskilled, but essential jobs; additional payment for extra burdens such as endurance of uncomfortable procedures	(a) Recognizes contributions of participants. (b) Uniform payment across studies. (c) Equal pay for equal work. (d) Less risk of undue inducement.	(a) May have little impact on recruitment. (b) Might undercompensate some subjects in relation to regular wage and preferentially attract others.
Reimbursement	Reimbursement	Expenses incurred (transport, meals, lodging); with or without reimbursement for lost wages	(a) Makes research participation revenue neutral. (b) Little risk of undue inducement. (c) Little or no financial sacrifice for subject if lost wages are reimbursed.	(a) May have little impact on recruitment. (b) Uneven reimbursement from subject to subject. (c) Reimbursement costs for high-salaried subjects may result in the targeting of low-income populations. (d) Financial sacrifice for subject if lost wages are not reimbursed.
Appreciation	Reward	Token of appreciation given at the conclusion of study	(a) Expresses gratitude for contribution made. (b) Not market dependent. (c) Avoids undue inducement.	(a) Likely to have no impact on recruitment. (b) No basis for consistency.

Ethical considerations

- **Undue influence *vs* lack of respect/exploitation**
- **Currently, tendency towards precaution**
  Hence, offers are kept low by RECs
- **Time for more 'fair' compensation/payment**
  - **Cfr research by Largent & Lynch, Aug 2017**
  - **Risk of undue influence is grossly overrated**
  - **Rather than assuming payments are too high, IRBs should start asking whether payments are high enough**
- **Time for 'ethical' compensation/payment**
  - **Cfr Gelinas *et al*., NEJM, Feb 2018**
  - **Central question is whether it is excessive or not**
  - **Authors propose a framework for ethical payment to research participants**

N ENGL J MED 378;8 NEJM.ORG FEBRUARY 22, 2018

A Framework for Ethical Payment to Research Participants

Luke Gelinas, Ph.D., Emily A. Largent, J.D., Ph.D., R.N., I. Glenn Cohen, J.D., Susan Kornetsky, M.P.H., Barbara E. Bierer, M.D., and Holly Fernandez Lynch, J.D.

Box 1. Considerations for Investigators Proposing Payment Offers

- Clearly communicate the rationale for payment amounts to the IRB by itemizing payments according to the following categories: reimbursement for out-of-pocket expenses, compensation for time and burdens, or recruitment incentive. Include justification for specific amounts proposed.
- Focus first on treating participants fairly by reimbursing and compensating them for participation before assessing whether incentive payments are needed.
- Plan to reimburse participants for out-of-pocket expenses unless there are strong countervailing reasons against doing so.
- Consult with the IRB on what types of expenses and amounts the IRB considers reasonable for reimbursement.
- Consider compensating participants for their time commitment and the burdens they assume.
- Provide justification for why the compensation rate proposed should be considered fair, drawing analogies to nonresearch contexts such as employment.
- Propose payment as a recruitment incentive only when proposing to offer more than would be justified for reimbursement and compensation.
- When possible, offer options for insurance coverage for participants (or other mechanisms of financial protection) in order to compensate for reasonable expenses arising from research-related injury.
- When compensation or recruitment incentive is offered, consider increasing safeguards around participant comprehension and informed consent, particularly as payment amounts increase. Include measures to assess comprehension (e.g., having participants explain key aspects of research in their own words) as appropriate.

Box 2. Considerations for IRBs Reviewing Payment Offers

- Keep in mind the distinction between "mere" and "undue" influence and recognize that payment can be an acceptable motivation to participate in research.
- Consider whether additional emphasis on the consent process, such as mechanisms for ensuring comprehension, would address concerns that payment might distort judgment or voluntariness and thereby undermine informed consent in particular cases.
- Recognize the importance of a risk–benefit determination in protecting participants and ensure that concerns about payment do not reflect underlying discomfort with the risk–benefit ratio.
- Recognize the positive ethical reasons in favor of payment that are based on fairness to participants and the importance of trial completion, which makes possible generalizable knowledge.
- Encourage or require investigators to itemize payments according to the following categories: reimbursement for out-of-pocket expenses, compensation for time and burdens, or recruitment incentive, with appropriate justification for the amounts proposed.
- Permit investigators to reimburse participants for reasonable out-of-pocket expenses or a reasonable estimate thereof.
- Consider developing standard operating procedures on the types of expenses and amounts considered reasonable for reimbursement.
- When evaluating compensation for time and burdens, focus on what would be considered a fair wage for similarly burdensome and risky nonresearch endeavors, such as employment, in the particular locale. Note that if a compensation rate is fair, it should not raise concerns about undue influence.
- Encourage or require investigators to offer payment as a recruitment incentive only when they wish to offer more than would be reasonable and fair for reimbursement and compensation.
- Recognize the positive ethical reasons in favor of facilitating recruitment through the use of recruitment incentives.

Regulatory texts

- **CTs Directive (EU)/Law on experiments (BEL)**
  - **Minors/Incapacitated adults (*extended to others*): no incentives or financial inducements are given, except compensation for travel costs, loss of earnings, pain, discomfort, etc.**
  - **EC gives OK on amounts and arrangements for rewarding and compensating subjects**
- **CTs Regulation (EU)/ Law on CTs (BEL)**
  - **No undue influence, incl. that of financial nature, is exerted on subjects to participate in the CT**
  - **Similar text for minors/incapacitated + legal rep, pregnant and breastfeeding women**
  - **Also acceptable: accommodation costs, costs for accompanying person, small token of appreciation**
- **France**
  - **Amount received per year can not exceed 4500 EUR (non taxable, Arrêté Min. 25 Apr 2006)**

Guidance documents

- **International**
  - **Nothing mentioned in the Declaration of Helsinki**
  - **CIOMS (WHO/UNESCO) Ethical guidelines (2016) GL 13: Reimbursement and compensation for research participants**
- **USA**
  - **FDA Information Sheet (revised 25 Jan 2018)**
  - **NIH Clinical Center guidance for compensation of research participants**
  - **Several research institutions/Universities/IRBs**
  - **Pharmaceutical companies**
- **Europe**
  - **UK/NHS HRA Ethics Guidance Payments and incentives in research (2014)**
  - **EUPATI (2015)**

Selection of guidance statements

CIOMS Ethical Guideline 13

... In addition, participants must be appropriately compensated for the time spent and other inconveniences resulting from study participation. The amount of compensation should be proportional to the time spent for research purposes and for travel to the research site. This amount should be calculated using the minimum hourly wage in the region or country as a reference value.
In Belgium, currently around 10 EUR.

NIH Clinical Center guidance

... The CC's 'Inconvenience Unit Guidelines' suggest unit levels for various procedures. ... Procedures are assigned a numerical value that is multiplied by 10 USD.
Examples:
- Blood sample: 2 units, urine sample: 1 unit
- Questionnaire (1h): 3 units
- MRI scan, lumbar punction: 5 units

NHS HRA Ethics Guidance

... Where patients are invited to take part in non-therapeutic research as 'patient volunteers' (*added, with no prospect of direct benefit*) they should be treated as 'healthy volunteers' with regards to payment.

Guidance documents

- **Belgium:**
  - **Order of physicians**
    - **2004: Compensation for direct costs and loss of income is OK, but may not lead to undue influence**
    - **2008: Amounts for HV should not be mentioned in study advertisements, but should be mentioned at 1st contact (ICF)**
  - **FPS Finances/Rulings**
    - **2010: Compensation for study-related expenses (e.g. for travel, parking, lunch, drinks) is OK > amounts not taxable**
    - **2015: Compensation for time investment is also OK, and received amounts are not taxable**

Truth in Advertising: Disclosure of Participant Payment in Research Recruitment Materials

Therapeutic Innovation
& Regulatory Science
2018, Vol. 52(3) 268-274

DOI: 10.1177/2168479018770644
tirs.sagepub.com

Recommendations

(based on OHRP & FDA guidance)

- It is ethically acceptable and indeed in many cases desirable for recruitment materials to disclose the payment amount offered and to state clearly the conditions under which participants will receive that amount.
  - The ethical reasons in favor of disclosing payment amounts stem from the positive role this can play in improving participation rates, which has strong ethical as well as practical importance.
  - These ethical reasons outweigh the potential risks of attracting populations more prone to undue influence and/or deception, once proper mitigation measures for these risks are in place.
- Information about payment should not be "exaggerated" or presented in a way that misleadingly implies that a patient will receive money that is not guaranteed to them.
- Regulatory guidance warning against "emphasizing" payment information on recruitment materials should be clarified to indicate that payment information should be no more prominent than the most prominent *non-payment* information on recruitment materials, although it may be more prominent than some non-payment information.

Current practice in Belgium: Analysis of 231 clinical trials

General findings

- **CT characteristics are comparable to FAMHP and international CT registry data**
  Thus, a representative sample of CTs in Belgium
- **If compensation for participation is offered, it is essentially (97 %) under some form of payment**
  Ex. of rarely used forms: educational material, training advice, course credits, extended access to study treatment
  The prospect of therapeutic benefit is not mentioned as such
- **Wide variety in trials > wide variety in practices**
  - **In 13 % of CTs, all in pts, 90 % non-comm.: no payment at all**
  - **In 87 % of CTs, 90 % comm., some form of payment is offered:**
    - **In 67 % of cases, for travel expenses only**
    - **In 28 % of cases, for travel and other reasons**
    - **In 5 % of cases, for other reasons only**

Compensation/payment practices

- **CTs in HV only (18 trials, 8% of total)**
  - **10 of them IITs sponsored by academia**
  - **HVs always received some form of compensation, for travel expenses, time investment and inconvenience/burden**
  - **Commercial sponsors offered higher amounts than academic sponsors for similar time spent and burden**
  - **ICFs were fairly detailed about amounts and reasons, while recruitment material was less precise ('fair' compensation, amount per day, total amount only once)**
- **CTs in patients (213 trials, 92% of total)**
  - **In 180 of these trials (85%), patients were compensated for travel expenses**
  - **In 18% also for meal costs, in 7% also for time spent, in 4% also for discomfort, and in 2% also for loss of earnings/vacation (all for parents of children)**
  - **In 5 trials overnight stay in an hotel was also paid for (max of 200 EUR per night), in 2 for parents of children**
  - **ICFs were not always explicit: often, 'ask inv. for more details'**

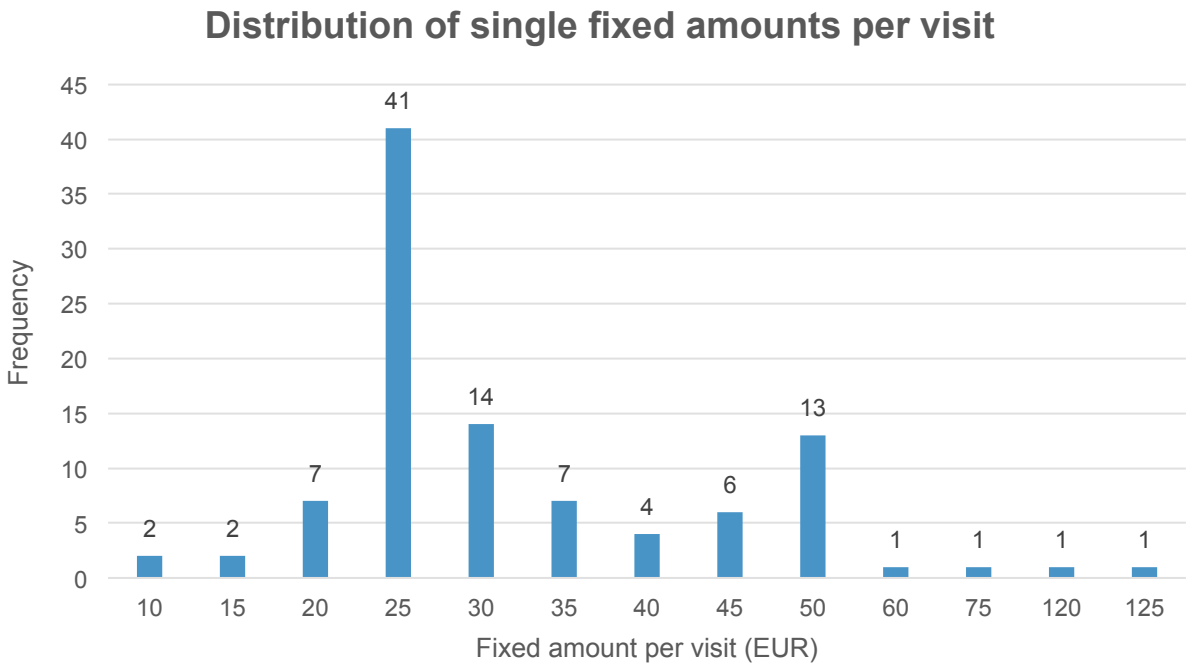
Disparity in payments for ‘travel expenses’

- **In 68% of cases a single fixed lump sum is offered per visit, but this can vary from 10 to 125 euros (cfr next slide)**
- **In 15% of the trials a fixed amount per visit is offered depending on the distance travelled (to and from the centre) In 64% of cases, 25 EUR < 100 km and 50 EUR > 100 km is offered in 14% of cases, 50 EUR < 100 km and 100 EUR > 100 km and in 22 % of cases, even higher amounts**

▸ This suggests, as confirmed by some of our interviewees, that these fixed amounts not only compensate for travel, but probably include hidden payment for other reasons not mentioned (in the ICF)

- **In 10% of the trials, travel expenses are reimbursed based on receipts and tickets to be kept by the participant**
- **In 7% of the trials, the cost of the exact travelled kms is reimbursed according to the official per-km allowance (currently 0.3573 EUR/km)**

Disparity in payments for ‘travel expenses’



Current thinking in Belgium: survey of 36 reps of 11 stakeholders

8 CT participants as HV	4 CT participants as patients
3 Clinical researchers	2 Research nurses
3 Staff members of ph 1 units	2 Staff members of CTCs
4 Members of research ECs	2 Bio-ethicists
4 Reps of commercial sponsors	3 Reps of non-commercial sponsors
1 Staff member of a CRO	

Selection of opinions and experiences

- **Clinical trials in HV**
  - **Healthy volunteers:**
    - **Their main motivation to participate in CTs is money**
    - **Another important factor is the time period to be available for the trial**
    - **Some of the volunteers would not participate in too risky studies**
    - **Most of them are loyal to one centre (feeling of safety and trust)**
  - **Phase 1 centres:**
    - **Most important criteria are time investment and inconvenience**
    - **Practices vary between centres, but are thought by the representatives to be relatively similar**
    - **Not willing to share their methodology > initiative from BAPU?**
  - **Ethics committees:**
    - **Lack practical recommendations**
    - **Would welcome some harmonisation**
    - **Plead for a pan-European fool proof system to avoid excessive and unsafe participation in consecutive clinical trials**

Selection of opinions and experiences

- **Clinical trials in patients**
  - **Patients:**
    - **Participation mostly based on hope of a therapeutic benefit and altruism**
    - **It should not cost them anything**
    - **Would welcome more respect as partners in research**
      'Patient centricity' should be more than a buzzword
    - **Appreciation of compensation is different according to health status, or age, or whether they are still professionally active**
  - **Clinical trial centres (investigators, research nurses, CTC members):**
    - **Feeling of sometimes being sandwiched between sponsor and EC**
    - **Find variability between departments within one centre unwise, and would welcome some harmonisation**
    - **Study coordinators find it easy to work with vouchers**
    - **Some found that the fixed amounts per visit should be updated, as they seem to remain the same since many years**

Selection of opinions and experiences

- **Clinical trials in patients**
  - **Ethics committees:**
    - **Still relatively conservative with fear for undue influence**
    - **Compensation as incentive (for recruitment) is not appreciated**
    - **If confronted with the idea of 'undercompensation' of patients, most interviewed members are willing to reconsider this and would welcome an initiative to issue some guidance (from BAREC?)**
  - **Sponsors:**
    - **Commercial sponsors (and CROs) have no major issue with this topic, and claim to be mostly receptive to recommendations from ECs**
      More disparity of opinion on post-trial availability of beneficial tested treatments (till when: market access or reimbursement in Belgium?)
    - **Non-commercial sponsors seem to be more reluctant to accept a change in attitude towards (higher) payment of patients**
      Reasons cited: lack of budget, altruism should remain key, patients are sufficiently compensated by getting early access to new treatments

Discussion on the findings: overall

- **Research data are scarce and predominantly from USA**
- **In USA/UK, there's a shift in thinking about the topic:**
  - **Risk of undue influence is seen as grossly overrated**
  - **Fair compensation/payment is considered ethical for all participants in clinical research**
  - **Recruitment materials can disclose amounts offered**
- **The 4-model concept (cfr. Dickert & Grady) is a sound basis for an ethical framework (cfr. Gelinas *et al.*) and for workable guidelines (cfr. CIOMS, NIH CC, UK NHS/HRA)**
  - **Reimbursement of all study-related expenses should be the general rule Participants should not have to pay for making a contribution to the social good of research > Participation should be revenue neutral Exceptions permitted or not? If yes, strong rationale needed**
  - **Compensation for time (based on minimum wage), inconveniences and burdens (cfr NIH CC guidance) is more controversial Consensus for HVs, acceptable for patients in non-therapeutic research, but less so for other patients**
  - **A token of appreciation is particularly suitable for children, or research without important time investment and inconvenience, and also for sampling of bodily material for future research**
  - **Incentives for participation (recruitment or study completion bonuses) are the most controversial category of payments, but may be legitimate in certain circumstances**
  - **But alternative compensation mechanisms should also be considered, e.g. early and continued access to new beneficial treatments**

Discussion on the findings: Belgium

- **There is a wide diversity in practice**
  - **Within one research centre, one department, one category of expenses, …**
  - **Between healthy volunteers and patients, between types of sponsors, between phase 1 centres (and probably between hospitals), …**
  - **Not different from other countries**
- **And also divergence in opinions**
  - **Between and even within categories of stakeholders**
  - **Some people have strong feelings about some topics, while others are more reasonable and open to discussion**
  - **Anyhow, there seems to be room for concertation between stakeholders and for some harmonisation**
- **Therefore:**
  - **Our exploratory research could serve as an eye-opener**
  - **Together with the overall paradigm shift in thinking and the pressure for harmonisation within the upcoming new clinical trial legislation**
  - **This seems to be the right moment to start thinking about possible improvements in current practice**

Proposals for a way forward in Belgium

- **This exploratory research will be extended**
  The results will be made wider known and discussed
  - **More interviews and discussion forums are/will be organised (including French speaking stakeholders)**
  - **Results are currently presented to different stakeholders and will be published in a scientific journal**
- **More harmonisation and written guidance would be welcome**
  - **BAREC is interested, in collaboration with BAPU and others?**
  - **Such an initiative would come at the right time in view of the new law on clinical trials (applicable in 2020) Therefore, also in collaboration with the CT College**
  - **Objective: create a minimal set of recommendations, reflected also in the ICF templates under revision**

Thank you

Time for questions, your thoughts, experience and opinions