Belgian Association of Research Ethics Committees (BAREC)

Guidance on fair compensation of subjects for their participation in clinical research in Belgium

Authors: BAREC Working Group on Compensation (cfr Appendix 1)

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1. Context

Compensating subjects for their participation in clinical research is currently still a much debated ethical issue. Reimbursing research participants for their study-related expenses is widely agreed as a right, fair and acceptable practice, but compensating them for other reasons, such as for time investment and inconvenience, or for their willingness to participate, is still more controversial.
Overall, guidance documents on this topic from regulatory authorities, research institutions or Human Research Ethics Committees (ECs) are scarce, and only very general in nature.
The ethical controversy on the issue and the absence of detailed guidelines leads to a wide variety of standards and practice, also in Belgium. Therefore, a national initiative providing practical guidance, with broad support of all stakeholders, would be welcome.

2. Objective

This Guidance provides recommendations for fair compensation of subjects for their participation in clinical research in Belgium ("Guidance"), and is issued by the Belgian Association of Research Ethics Committees (BAREC). The objective is to present a common framework with practical guidance of interest to Ethics Committees (ECs), sponsors, investigators and participants involved in clinical research in Belgium. These recommendations will hopefully contribute to more harmonisation of current and future practice regarding compensation of research participants in Belgium.

3. Workflow

Four preliminary versions of the document were drafted by the members of the BAREC Working Group on Compensation ("WG", list of members in Appendix 1). During this process, they also received input from other members of their ECs, especially with expertise not represented in the WG. Draft 4 was sent to all member ECs within BAREC, with a request for comments and suggestions. A revised pre-final version was submitted to the BAREC Board for approval, and the final version is available on the BAREC website. It will be updated as needed.

4. Terminology and abbreviations

4.1. Definition of terms used

Clinical research
All categories of clinical research involving human subjects (healthy volunteers or patients), requiring a positive opinion of an appropriate EC in Belgium. More details can be found in section 6.1.

Compensation
General term reflecting something given to research participants to make up for expenses, time investment, inconvenience, and willingness in relation to their participation in clinical research. It does ***not*** refer to indemnification for research-related injury, e.g. no-fault compensation; and it does ***not*** refer to study-related costs legally to be borne by the sponsor, such as all costs of the intervention(s) investigated, investigational site visits or admissions, investigations and procedures, and co-treatments required by the study protocol.

In this Guidance thus, the broader term compensation includes all kinds of indemnification of subjects for their participation in clinical research, e.g. reimbursement of study-related expenses (defined below); making up for time investment, loss of income or inconvenience; as an incentive (defined below); or as a token of appreciation.
Compensation can either be offered in financial or monetary forms, i.e. as payment (further defined below), but also includes indemnity forms of non-financial nature, either provided as goods (e.g. book, goody bag, or toy) or services (e.g. course credit, personal advice).

Incentive
In this context, an inducement to motivate a subject to participate in a clinical research project, or to maintain his/her participation in the study (till its completion). It is forward looking in nature.

Payment
Compensation restricted to financial or monetary forms, e.g. bank transfer, cash payment, gift certificate or voucher.

Reimbursement
The act of compensating research participants for their study-related out-of-pocket expenses, e.g. for travel, meals or accommodation, by giving them an amount of money equal to what was spent.

Undue influence
Undue influence, according to the Belmont Report (US Department of Health & Human Services, 1979), occurs 'through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance', i.e. agreement to participate in clinical research. The US Office for Human Research Protections (OHRP), in its recommendation 'Addressing Ethical Concerns Regarding Offers of Payment to Research Participants', considers compensation/payment as undue influence 'when it could compromise a prospective subject's examination and evaluation of the risks or affect the voluntariness of his or her choices'.

4.2. Abbreviations

A list of abbreviations can be found in Appendix 2.

5. Background

There are 3 main reasons why guidance on compensation of subjects for their participation in clinical research in Belgium seems indicated, and why BAREC took the initiative to issue this Guidance. They are briefly presented in this section, but more detailed information can be found in Appendix 3.

First, there is still debate about some ethical aspects of compensation, such as:

- Whether not offering any compensation at all is ethically fair and acceptable.
- Offering incentives to subjects to (continue to) participate in a clinical study.
- The risk of undue influence in paying research participants.
- Compensating patients the same way as healthy volunteers.
- Whether academic research should be similarly treated as commercial research.

In sections 6 and 7.1., we present the consensus view of the member ECs of BAREC on these considerations that served as the basis for the recommendations made in this Guidance.

Secondly, the current publicly available guidance on this topic is scarce and very general in nature. The most specific guidance comes from the EU Clinical Trials Expert Group (CTEG) in their document entitled 'Compensation of trial participants' (Eudralex 2020/2), which simply states that acceptable compensations for trial participation include travel, accommodation and meal costs (also for the legal representative or the accompanying person), loss of earnings, discomfort and suffering. In addition, some provisions/requirements are mentioned for financial incentives and conditional compensation in order to be acceptable.

It is up to the assessing EC to agree on the appropriateness of providing compensation to research participants, as well as on the amounts and arrangements proposed. As the ECs seem to struggle with the practical implementation of these general recommendations, more explicit practical guidance is considered more than welcome.

And finally, current practice in Belgium is very diverse and could benefit from some harmonisation. Since the implementation of the EU Regulations regarding clinical trials (CTR), medical devices (MDR) and *in vitro* diagnostics (IVDR), the sponsor of a clinical research study falling under these regulations (and the corresponding Belgian laws) can no longer choose the evaluating EC. For each individual study application, the evaluating EC will be appointed by a national body (the Clinical Trial College), and should be independent of the investigational centres involved in the study. It is expected that this new legal procedure may lead to even more diversity in implementing compensation of research participants in practice. Hence, harmonised guidance supported by all Belgian ECs concerned seems warranted.

6. Scope

6.1. Types of clinical research

All clinical research involving human subjects (healthy volunteers or patients) legally requires a positive opinion of a recognized EC in Belgium before the start or a modification of the clinical research.
This includes:
1°/ Interventional clinical research, concerning:
- Investigational medicinal products, defined as 'clinical trials' in the CTR and the corresponding Belgian law (2017).
- Medical devices, defined as 'clinical investigations' in the MDR and the corresponding Belgian law (2020).
- *In vitro* diagnostics, defined as 'clinical performance studies' in the IVDR and the corresponding Belgian law (2022).
- Interventions not regulated in the 3 previous EU regulations and their corresponding Belgian laws, but qualified as 'experiments' in the Belgian law of 2004 related to experiments, such as studies that test surgical techniques or that impose changes in human behaviour (physical training for instance).
2°/ Prospective non-interventional clinical research, which also qualifies as 'experiments' in the same Belgian law (2004) related to experiments.

This Guidance is **not applicable to** research on already available human bodily material (although also legally requiring a positive opinion of an EC in Belgium) or research making secondary use of already available personal data (qualified as 'retrospective studies' but not as an 'experiment' in the Belgian law of 2004 related to experiments, and thus not legally requiring a positive opinion of an EC).

6.2. Types of sponsors

In principle, the rules governing compensation of research participants should be similar for clinical research sponsored by commercial sponsors as for clinical research sponsored by academia or not-for-profit funders. This is also the consensus view of the ECs members of BAREC .

6.3. Eligible subjects for compensation

In principle, all participants in clinical research should have equal rights to compensation, whether they are patients or healthy volunteers. This is also the consensus view of the ECs members of BAREC.
Additionally, the research participants' appropriate representatives, companions, guardians or supervisors, such as parents, a legal representative, or a caregiver, should receive proper compensation as well.

6.4. Reasons for compensation

Subjects can be compensated for their participation in clinical research for different reasons:

6.4.1. Study-related expenses

Study-related expenses concern, for example, expenses for travel to and from the investigation centre, for food and drinks during long centre visits, for babysitting if needed, as well as for nearby accommodation if required.
Whether certain expenses or costs are to be considered study-related may sometimes lead to discussion with the sponsor. In our view, and without limitation, mandatory or recommended use of (a specific form of) contraception or of a sun blocker, or adherence to a specific diet, should as a rule be considered as study-related. The same applies to mandatory or recommended cryopreservation of oocytes or sperm.

6.4.2. Loss of earnings, time Investment

Although the terminology 'Loss of earnings' is used in the legislation, this reason for compensation is potentially better qualified as 'time investment'.

6.4.3. Burden, discomfort, or inconvenience

Some investigative procedures, examinations, tasks or restrictions can be considered burdensome to clinical research participants, and may lead to some form of compensation.
On the FAMHP website on clinical investigations (MDR), a guidance document can be found that covers the topic "Which procedures in clinical investigations are considered burdensome or invasive?". Examples of burdensome procedures are sedation, invasive cardiac procedure (catheterization, stent, angioplasty), blood tests, etc. Examples of non-burdensome procedures are patient surveys, thermography, …

6.4.4. Willingness to participate

Compensation for willingness to participate can be used either as a token of appreciation, or as an incentive for recruitment or retention in the study.

Attention:

It is the consensus view of the ECs members of BAREC that research participants cannot be compensated for risk taken.

It is the consensus view of the ECs members of BAREC that a study can only take place if the benefit-risk ratio of such study is positive, meaning that the risks for the individual study participants cannot be higher than the potential benefits for such participants. In other words: studies where a specific risk could be compensated separately because the benefit-risk ratio is negative, are to be considered unethical and should not be carried out in the first place. Offering additional compensation to candidate participants for such studies does not change the unethical character thereof and can therefore not be accepted.

6.5. Modalities of compensation

Compensation can be in the form of a monetary transaction, e.g. payment of a certain amount, gifts of a certain value (voucher, gift card, cinema ticket, etc.), or can be of non-monetary nature, e.g. offered as goods (e.g. goody bag, toy, book, study device or app) or as a service (e.g. personal health advice, results of specific tests).

7. Detailed guidance

7.1. BAREC's position on some debated ethical concerns

Compensating subjects in exchange for their participation in clinical research is in fact not mandatory, but it is now generally considered an acceptable practice.

The basic ethical principle should be that participating in clinical research shouldn't cost the participants anything (on top of standard of care costs, if applicable).

Therefore, it is our view that, as a general rule, all study-related expenses (cfr section 6.4., paragraph 1.) should be reimbursed (when advanced by the participant) or compensated for (when a reasonable fixed lump-sum has been agreed upon). This should be the case for all clinical research within the scope of our Guidance, and should be independent of the type of sponsor (commercial or non-commercial) or the type of participants (patients or healthy volunteers).

Additional compensation, such as for time investment, inconvenience, or willingness to participate (cfr section 6.4., paragraphs 2, 3 and 4) can be offered, but should be well-justified.

It is the consensus view of the ECs member of BAREC that such compensation is more easily justified in clinical studies of interventions without (sufficiently) proven therapeutic benefit, i.e. in early phase clinical development, such as in human pharmacology studies (e.g. First-in-Human trials or other phase 1 studies, both in healthy volunteers or patients) or exploratory safety and efficacy studies (e.g. phase 2a dose-response or Proof-of-Concept studies), according to the definitions used in ICH guideline E8(R1) (ICH, 2021).

In sections 7.2.2/3/4 more detailed information on these topics can be found.

Note: BAREC's view on applying the same rules for (i) academic or not-for-profit sponsors versus commercial sponsors, and/or for (ii) patients versus healthy volunteers, were also expressed in sections 6.2 and 6.3 respectively.

7.2. Fair amounts of compensation

In this section, only monetary amounts (in euro) are specified for each reason for compensation.
They can be paid as such, i.e. by bank transfer or in cash, or, alternatively, an equivalent amount can be made available as a gift card, a voucher, or a ticket. When non-monetary forms of compensation are proposed instead, they should represent an equivalent amount.
As expenses or costs may vary according to geographic region, these amounts may vary between participating centres, although such differences should be rather small within Belgium.
All amounts recommended are valid for 2023. Whenever possible, a reference is already added.
The recommended amounts can be revised annually on the basis of the evolution of the Belgian consumer price index (Statbel, 2023)/cost of living.

7.2.1. Compensation for study-related expenses/costs

In general, reimbursement of real study-related expenses/costs is recommended. This is preferred by tax controllers, but may lead to burdensome administrative hassle for the investigational site staff.
If, alternatively, compensation is offered as a fixed amount or lump sum, they should be substantiated with examples of real costs at the investigational site or average costs in the region where the research centre or the participant is located.
As stated before, if the sponsor does not want to bear the costs of some of the study-related expenses or costs cited below, this should be clearly justified in the application dossier that the sponsor submits to the EC for review. If the assessing EC agrees with such an exemption, this should also be clearly stated in the Informed Consent Form (ICF), so that a potential participant can judge well-informed to participate or not.

Travel

Costs for travel from home to the investigational centre and back, can be compensated by:
- Reimbursement of real expenses, e.g. ticket(s) of public transport, a car parking ticket, or taxi fare receipt(s) if judged appropriate.
- A mileage allowance per km, preferably at the official rates published each year by the Federal Public Service Finance. The car allowance 2023, valid from 1 April 2023 till 30 June 2024, equals 0.4246 euro per km (Moniteur Belge, 2023). The bike allowance for the fiscal year 2023 equals 0.25 euro per km (SPF Finances, 2023).
- A fixed amount or lump-sum payment.

Although compensation for expenses is not subject to income tax in Belgium (see Section 7.5 for more details), tax controllers may argue that a lump-sum payment may deviate too much from the real expenses. Therefore, attention should be paid to whether or not the proposed lump-sum amount is in fact realistic and reasonable.

Here, an example is recommended of a reasonable schedule that should pose no problem. The amounts are calculated according to the following formula: highest number of km in the range, times the official car allowance per km (0.4246 EUR in 2023), plus 10 EUR for parking, rounded to the nearest 5 or 10 EUR. Over 200 km, the real number of km is used in the same formula.
However, any other realistic modality of lump-sum calculations can be agreed upon, if properly justified. This table, or a similar one, should be part of the information provided in the informed consent form (ICF).

Table 1: Fixed amounts for travel expenses	
Roundtrip in km	**Amount in euro**
Up to 25	20
26-50	30
51-75	40
76-100	50
101-125	65
126-150	75
151-175	85
176-200	95

In Belgium, reimbursement of air fare tickets is uncommon, but could be justified in certain circumstances, e.g. to allow the participation of non-Belgian residents in clinical studies taking place in Belgium where patients with orphan diseases are recruited, or to allow participation of non-Belgian residents in clinical studies conducted by/in a Belgian investigational centre that is designated as centre of excellence in a certain field. For such participants (and their accompanying person, if needed), reimbursement of a return trip by air in economy class could be deemed acceptable by the assessing EC.

Food and drinks

For study centre visits lasting over 4 hours, and especially when the participant had to fast before any such visit, a meal or a compensation for a meal and drink(s) should be provided. This should also be the case for their accompanying person, if help is needed.
The most practical solution is to provide a reasonable lump-sum payment, e.g. 15 EUR in 2023, equivalent to the average cost of a sandwich, some fruit and a drink. Another amount can be acceptable, if justified by the average price of a simple meal in the cafeteria of the investigational centre.

Accommodation

If, for well-argumented reasons, accommodation or lodging near the investigational centre during 1 or several days is foreseen in the study protocol for the participant and, if needed, for their accompanying person, then 2 options are acceptable, either:

- Payment of a fixed amount, corresponding to the average budget price of a double hotel room in Belgium, which is 120 EUR in 2023 (Budget Your Trip, 2023).
- Reimbursement of the real costs, limited to the fixed amount mentioned here above, except when a higher amount is justified due to a more expensive geographic location or high-season rates.

Babysitting

This can be considered whenever a research participant is unable to leave a young child (or children) or another helpless cohabitant alone at home during study visits to the investigational centre.

For this service, the average hourly rate for a babysitter in Belgium in 2023 is 8.63 EUR, ranging per province between 8.21 in Namur and 9.20 EUR in Brussels (Webpage Babysits, 2023). The mean day price for childcare in Belgium is +/- 30 EUR (Parentia, 2023).

Study-imposed changes in behaviour or usual habits

Examples within the category of study-imposed changes in behaviour or usual habits are:

- Mandatory (change in) in contraceptive measures, for participating women of child-bearing potential (WOCBP), fertile male participants, and their (non-)pregnant WOCBP partner, according to the current guidelines (CTFG, 2020 and EMA, 2022). In addition, the cost of monthly pregnancy tests during the contraceptive period in WOCBP should also be borne by the sponsor.
- Compulsory use of sun protection (sunscreen or sun blocker).
- Required adherence to a specific diet if such diet is expensive.

In these cases, the most practical solution is to reimburse the real costs.

Cryopreservation of oocytes or sperm

If cryopreservation of oocytes or sperm is recommended before starting the study for participating WOCBP or fertile males with a desire to have a child/children in the future, then the costs therefore should be borne by the sponsor. Reimbursement of the real costs is the most practical solution.

7.2.2. Compensation for time investment

In legal texts, compensation for 'loss of earnings' is mentioned as an acceptable practice (cfr. Section 5.2). Here, this is qualified as compensation for 'time investment', as it is not the objective to compensate for the real salary loss that a participant may be suffering during the time spent at the research centre. The opportunity to participate in clinical research is not in any way dependent on the amount of salary one earns. Hence, the international consensus is to compensate time investment on the basis of the national minimum wage (NMW), rather than based on the real wage or revenue of the participant.

The current gross NMW for adults in Belgium, since December 2022, is 1955 EUR per month for a 38h work week (Wage Indicator Foundation, 2023), i.e. about 13 EUR per hour.

Compensation for time investment is fairly well introduced in healthy volunteers, as well as in patients participating in clinical research without expected therapeutic benefit, i.e. exploratory early phase studies. It is far less common practice when it comes to patients participating in confirmatory late phase studies, arguing that participants in these studies have a far greater chance to benefit from the

experimental or comparative standard-of-care (SOC) intervention. Therefore, extra forms of compensation are considered by some as not being needed.
Here it is recommended that as a rule longer time investment (over 2 hours spent at the investigational centre) is compensated for all participants, except when well justified, and agreed upon by the assessing EC.

7.2.3. Compensation for burden, discomfort and inconvenience

It is generally agreed that compensation for burden, discomfort and inconvenience is acceptable, but as it is difficult to estimate in monetary value, detailed guidance on this topic is lacking, and there is not much information available on its actual practice.
When it is proposed to participants, it is often not stated as such in the ICF, but included in a lump-sum amount for participation without a breakdown for the different reasons. This practice, however, is not recommended.
Instead, it is recommended to compensate for burdensome study procedures or investigations by a fixed reasonable amount, e.g. 50 EUR for a gastroscopy, 70 EUR for an arterial catheterisation.

7.2.4. Compensation for willingness to participate

As compensation for willingness to participate, essentially 2 forms are distinguished: as a token of appreciation on one hand, and as incentives, rewards or bonuses on the other hand.

Token of appreciation

As a token of appreciation, 2 approaches are frequently practised:

1°/ Items, goods or services of relatively low value
Items, goods or services of relatively low value are especially suitable to compensate children directly, independent from their parents or legal representative. They are also often proposed to students or participants in studies using qualitative research methods that are not very time-consuming nor very burdensome, such as taking an interview, filling out some questionnaires, or participating in a focus group.
Examples are numerous: e.g. a ticket for a visit to a cinema or an entertainment park, a gift card, a subscription (limited in time) to a music or video streaming platform, a games app, a goody bag, a toy, a book, or a small lump-sum.
It is recommended that the value of these items does not exceed 50 EUR.

2°/ Items, goods or services with higher (non-material) value
Another category of compensation concerns items, goods or services with higher (non-material) value. This category comprises several forms of compensation that might be considered valuable by research participants, such as post-study drug availability making specific study test results available that can be useful in the future, giving training advice to sportspersons or athletes, leaving a beneficial experimental implantable medical device in the body, keeping a medical device or app used in the study (or purchased at a discount), and course credits for students. The precise value of these forms of compensation is difficult to estimate. They are often appreciated as extremely useful and valuable by the participants, so much so that they might more easily accept not to be extra compensated for, for instance, study-related expenses or time investment. In general, this practice is considered to be acceptable.

Incentives, rewards or bonuses

Incentives, rewards or bonuses are sometimes proposed to (potential) research participants in order to stimulate study recruitment, study retention or study completion.

This practice should be carefully reviewed, as it may induce undue influence. However, there may be instances where an incentive of a reasonable value might be useful and acceptable, e.g. to stimulate the often very difficult recruitment of patients with certain orphan or rare diseases, to retain overly obese patients in a long-term study thus limiting an otherwise to be expected high drop-out rate, or to encourage participants in an event-driven study to stay in the study until the end in order to maximally support the chance of a robust statistical analysis and more meaningful study results.

It is recommended that the assessing EC evaluates each proposal on a case-by-case basis, and that the amount paid to a subject as an incentive remains reasonable without exerting undue influence.

7.3. Modalities of compensation

As already mentioned in the previous sections, compensation for participating in clinical research can be offered either in the form of a monetary transaction, such as payment of a given amount, or gifts of a certain value (e.g. voucher, gift card, ticket); or can be of non-monetary nature, offered as items or goods (e.g. book, goody bag, study device, toy) or services (e.g. course credit, training advice). It is primarily up to the sponsor and the investigational centre teams to decide which modality they find most suitable and practical, without too much administrative burden for both the investigational centre staff as well as the participants. Some centres may work with a processing fee to handle modalities of compensation with extra workload.

They should also propose an arrangement about the timing and conditions of offering payments. For short-term studies (a few days up to less than 3 months), it is acceptable to compensate or pay participants only at the end of their participation. For longer-term studies (as of 3 months), quarterly payments should be the rule, or, alternatively, per centre visit. If a subject is only participating in a particular phase of a study, or does not participate until the study is completed, a *pro rata* compensation or payment can be proposed, based on the actual time spent in the study and the actual number of investigations/procedures undergone.

A candidate participant who has been screened but finally not recruited, may be offered a specific compensation just for the screening.

As a general rule, the evaluating EC and the investigational centre (including the PI and the clinical trial centre) have to agree with the amounts, modalities and arrangements of monetary or non-monetary compensation proposed in the application dossier submitted to the EC and the reasons therefore. At some sites, for example, vouchers are not a recommended modality because of several reasons: it creates extra effort for the participant, it is often not clear in which stores the vouchers can be used, the vouchers can expire, there is a risk that the participant loses the voucher,.... Therefore, if the evaluating EC, site, sponsor and participant all agree on the use of the vouchers as modality of compensation, it can be used. To make this decision, the patient needs to be fully informed about the practicalities as well as the advantages and disadvantages of vouchers. An alternative should always be foreseen for participants who are not able to use or have difficulties with using vouchers (e.g. patients with Alzheimer, elderly, ...).

7.4. Information on compensation as part of the consent/assent process

Candidate participants to a particular clinical study should be well-informed about the study, so that they can decide entirely out of free will whether they will participate or not. The current guideline on Good Clinical Practice (GCP) outlines all that is needed for an adequate informed consent process (ICH, 2016), including all necessary information to clinical research participants in writing through the informed Consent Form (ICF) for adults, and the Informed Assent Form (IAF) for minors.
In advertisement material for recruitment, it is recommended not to mention detailed amounts of compensation offered, in order not to unduly influence candidates to participate. The information should be limited to for instance 'A fair compensation for participation will be offered'.
However, oral explanation as well as information in writing (ICF and IAF) should be as clear and explicit as possible. Therefore, it is recommended that this information should include:
- The different reasons for compensation (cfr Section 6.2), and whether compensation for each category is offered or not (cfr Section 7.1)..
- Per category for which compensation or payment is offered: for what exactly, under which form, and equivalent to which amount (cfr Section 7.2).
- The timing and conditions of payments (cfr Section 7.3).
- The provisions for privacy protection of the participants (cfr Section 7.6.3)
- The provision that the compensation offered is exempt from income tax declaration for Belgian residents, but that it might be different for residents of foreign countries (cfr Section 7.5).
For vulnerable participants, e.g. minors or incapacitated persons, the ICF for their parents or legal representative should give details on compensation to the participant as well as to the accompanying person. The information given to minors, as part of the assent process, should be adapted to their age and maturity.

7.5. Fiscal aspects

In Belgium, 4 advance tax rulings in relation to compensation offered to research participants have been published by the Tax Ruling Service, being part of the Federal Public Service Finance (FPS Finance, 2010, 2013, and 2015/1 and 2). The first one has been prolonged twice, the last time as of 1 July 2020 for another 5 years (FPS Finance, 2021).
These rulings clarify that such compensations, including for the time spent in the research centre (although not very clearly stated), are not to be considered as taxable income for the participant, as participation in clinical research is not considered to be a job or to generate 'diverse income'. On the part of the ultimate payer, they are considered as tax-deductible business expenses.
In principle, such tax rulings are only valid between the anonymous applicant and the tax authority for a limited period of time (usually 5 years, but can be prolonged). In practice, the provisions can be extended to similar situations, but be aware that tax controllers could still interpret the tax law differently. In addition, and as already mentioned before, if fixed amounts or lump-sums are used, they should be as close as possible to the real expenses or costs.
The laws mentioned above in this section 7.5 only apply to research participants who are Belgian residents. Residents from other countries participating in a Belgian centre in clinical research might fall under a different regime. For instance, residents from The Netherlands should include compensation for their participation in clinical research in their tax declaration. It should be clearly specified in the ICF that the research participant is responsible for this potential declaration.

7.6. Special issues

7.6.1. Vulnerable participants

Apart from the usual subjects qualified as vulnerable participants, such as minors, incapacitated adults, pregnant and breastfeeding women, other participants can also be very fragile, e.g. homeless persons, persons who inject drugs (PWID, formerly known as drug abusers), gambling addicts, and prisoners, all financially vulnerable people. Compensating these subjects can be very challenging, because these groups may be at a higher risk of undue influence. Any recommendation can only be general.

It is recommended that the stakeholders involved (investigators, knowledgeable organisations or institutions, evaluating EC), consult one another to discuss and agree on the most appropriate way to minimise undue influence, and to come up with a case-by-case solution depending on the specifics of the study and the vulnerability of the targeted population group.

7.6.2. Studies with fairly high amounts of compensation

Some types of clinical research studies can result in fairly high amounts of compensation offered to the participants. For instance, in longer term phase 1 and Controlled Human Infection Model (CHIM) studies, usually in healthy volunteers, the proposed compensation for time investment and inconvenience can amount to (several) thousands of euros. As an example, in the currently running COVHIC002 Coronavirus Human Infectious Challenge Study at the Imperial College London (UK), participants are offered 200 GBP per day of quarantine stay at the centre (Imperial College London, 2022).

Especially in these circumstances, the sponsor and the investigation site(s) should carefully detail and justify the proposed amounts and modalities of payment. It is up to the evaluating EC to carefully assess whether the compensation offered is considered fair and without undue influence. In Belgium, these phase 1 studies are evaluated by a limited number of specially recognised ECs with appropriate expertise in this field, which is expected to contribute to a somewhat harmonised attitude towards these studies.

7.6.3. Privacy issues

The act of offering monetary or non-monetary compensation to research participants should be handled in the strictest respect of privacy regulations, including the EU General Data Protection Regulation 2016/679 (“ GDPR”) (GDPR.EU, 2023), and, additionally, in Belgium, the Law of 30 July 2018 on the protection of individuals with regard to the processing of personal data (Moniteur Belge, 2018). This implies that the sponsor cannot have access to the identity of the participants, so that the transfer of money, gift cards, goods,services,... to the participants should be handled by the investigator/ the investigational centre, or a third-party service provider, each time also with respect to the legislation in force. Especially when third-party service providers are involved, such as Clincierge, Greenphire (ClinCard), Scout Clinical, or others, it is recommended that (i) the assessing EC has access to the arrangement between the sponsor and the service provider concerned, (ii) all parties involved declare that they will respect the applicable legislation on data protection, and that (iii) participants are well informed about the exact role of the selected service provider and the steps taken to respect their privacy.

7.6.4. Prize draws versus contests

When the number of participants in a clinical research project is high, sponsors are not always able or willing to compensate every participant. Then only a limited number of participants can be compensated by winning a prize.

Prize draws, such as a lottery or a raffle, in which the winner(s) is/are picked at random (by pure chance), are illegal in Belgium.

In contrast, a contest can be legally organised, in which participants can try to do something better than others. In this case, some skill is required to win a prize, for instance by using a simple tiebreaker question reachable for all participants.

If such a contest is organised to allocate compensation only to a limited number of participants, the contest rules should be adequate and submitted to the EC for agreement.

7.7. Overview document

It is recommended to sponsors of clinical research that they present all necessary information on compensation or financial transactions in an overview document as part of the application dossier. This can greatly facilitate the work of the assessing ethics committee.

For clinical trials, the template 'Compensation for trial participants', developed and endorsed by the EU CTEG, can be used (EudraLex, 2020/2).

8. References

Ambühl S, *et al*. Payment in challenge studies from an economics perspective. *J Med Ethics* 2020; 46:831-2.

Babysits. Wat is het gemiddelde babysit tarief in België? Accessed February 11, 2023. https://www.babysits.be

Budget Your Trip. How much do hotels cost in Belgium? Accessed February 11, 2023. https://www.budgetyourtrip.com/hotels/belgium-BE

Clinical Trials Facilitation and Coordination Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. Version 1.1. September 21,2020. https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf

European Medicines Agency (EMA). SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug. March 2, 2022. https://www.ema.europa.eu/en/documents/other/safety-working-party-recommendations-duration-contraception-following-end-treatment-genotoxic-drug_en.pdf

Eudralex-Volume 10-Clinical trials guidelines (1). Part II Document Harmonisation Guidance. November 2020. https://health.ec.europa.eu/system/files/2020-11/harmonisation_guidance_en_0.pdf

Eudralex-Volume 10-Clinical trials guidelines (2). Compensation for trial participants (Template). November 2020. https://health.ec.europa.eu/system/files/2020-11/payment_compensation_template_en_0.pdf

Eudralex-Volume 10-Clinical trials guidelines. Questions and Answers - Regulation (EU) 536/2014. December 2022. https://health.ec.europa.eu/system/files/2022-12/regulation5362014_qa_en.pdf

FPS Finance. Voorafgaande beslissing nr. 2010.091 dd 25.05.2010. Can be searched and printed from the website FisconetPlus : https://eservices.minfin.fgov.be
FPS Finance. Voorafgaande beslissing nr. 2012.488 dd 08.01.2013. Can be searched and printed from the website FisconetPlus : https://eservices.minfin.fgov.be
FPS Finance. Voorafgaande beslissing nr. 2015.075 dd 24.03.2015. Can be searched and printed from the website FisconetPlus : https://eservices.minfin.fgov.be
FPS Finance. Voorafgaande beslissing nr. 2015.254 dd. 16.06.2015. Can be searched and printed from the website FisconetPlus : https://eservices.minfin.fgov.be
FPS Finance. Voorafgaande beslissing nr. 2020.2209 dd. 13.01.2021. Can be searched and printed from the website FisconetPlus : https://eservices.minfin.fgov.be
GDPR.EU. General Data Protection Regulation. Accessed 13 February, 2023. https://gdpr.eu/tag/gdpr/
Gelinas L, et al. A Framework for Ethical Payment to Research Participants. N Engl J Med 2018; 378:766-771.
Grimwade O, *et al.* (1) Payment in challenge studies : ethics, attitudes and a new payment for risk model. *J Med Ethics* 2020; 46:815-26.
Grimwade O, *et al.* (2) Fair go : pay research participants properly or not at all. *J Med Ethics* 2020; 46:837-39.
ICH. Guideline for Good Clinical Practice E6(R2). November 9, 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
ICH. Guideline on general considerations for clinical studies. October 6, 2021. https://database.ich.org/sites/default/files/ICH_E8-R1_Guideline_Step4_2021_1006.pdf
Imperial College London. COVHIC002 Participant Information Sheet V 1.1 11.08.2022. https://www.imperial.ac.uk/media/imperial-college/medicine/infectious-disease/COVHIC002-Participant-Information-Sheet.pdf
Maris Y. Compensation/payment of subjects for their participation in clinical trials with medicines. Known ethical considerations, current practice in Belgium and opinion of different stakeholders involved. KU Leuven, January 24, 2018. Available upon request at: jrt_be@yahoo.com.
Moniteur Belge. Loi relative aux expérimentations sur la personne humaine. May 7, 2004. https://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=fr&la=F&cn=2004050732&table_name=loi
Moniteur Belge. Loi relative aux essais cliniques de médicaments à usage humain. May 7, 2017. https://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=fr&la=F&cn=2017050704&table_name=loi
Moniteur Belge. Loi relative à la protection des personnes physiques à l'égard des traitements des données à caractère personnel. July 30, 2018. https://www.ejustice.just.fgov.be/mopdf/2018/09/05_1.pdf#page=10
Moniteur Belge. Loi relative aux dispositifs médicaux. December 22, 2020. https://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=fr&la=F&cn=2020122240&table_name=loi
Moniteur Belge. Loi relative aux dispositifs médicaux de diagnostic in vitro. June 15, 2022. https://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=fr&la=F&cn=2020122240&table_name=loi
Moniteur Belge. Circulaire n° 717 – Adaptation du montant de l'indemnité kilométrique. March 16, 2023. https://docs.google.com/document/d/128IzA0FUlYhrSTxZh1F9bs63bNATPADj/edit

Official Journal of the EU. Clinical Trials Directive 2001/20/EC. April 4, 2001. https://health.ec.europa.eu/system/files/2016-11/dir_2001_20_en_0.pdf
Official Journal of the EU. Clinical Trials Regulation 536/2014. April 16, 2014. https://health.ec.europa.eu/system/files/2016-11/reg_2014_536_en_0.pdf
Official Journal of the EU. Medical Devices Regulation 2017/745. April 5, 2017. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745
Official Journal of the EU. In Vitro Diagnostic Medical Devices Regulation 2017/746. April 5, 2017. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0746&from=EN
SPF Finances. Indemnité vélo. Accessed February 11, 2023. https://finances.belgium.be/fr/particuliers/transport/deduction_frais_de_transport/trajet_domicile_travail/velo
Statbel. Consumer price index. February 11, 2023. https://statbel.fgov.be/en/themes/consumer-prices/consumer-price-index
US Department of Health and Human Services. National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. April 18, 1979. https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf
Wage Indicator Foundation/Loonwijzer.be. Minimumloon België. Accessed February 12, 2023. https://loonwijzer.be/loon/minimumlonen#:~:text=Het%20huidige%20minimumloon%20in%20Belgi%C3%AB,geldig%20vanaf%201%20december%202022.&text=Minimum%20Lonen%2C%20geldig%20vanaf%201%20december%202022

9. Appendices

Appendix 1: List of working group members

The BAREC Working Group on Compensation was composed of the following members:
- Ann Allegaert, member of EC AZ Groeninge: patient representative.
- Lien Decruy, member of EC AZ Groeninge: research coordinator.
- Patrick Evrard, BAREC Board member, member of EC CU Mont-Godinne: intensive care specialist.
- Patrick Miqueu, member of EC Bordet: bioethicist and biostatistician.
- Pieter Moons, BAREC Board member, member of EC UZA: biotechnologist and expert in biobanking.
- Isabelle Scheers, member of EC CU Saint-Luc: paediatrician and gastro-enterologist.
- Josse R. Thomas, former member of EC UZ/KU Leuven: pharmacist and clinical pharmacologist.
- Bert Vanderhaegen, BAREC Board member, member of EC UZ Gent & EC AZ Sint-Lucas Gent: moral theologian and bioethicist.
- Daphné Van de Wildebergh, former member of EC UZA as legal counsel.
- Katelijne Van Overwalle, member of EC UZ/KU Leuven: patient representative and former human resources director.
- Indra Verhaeghe, staff member of EC UZ/KU Leuven: biomedical scientist.

The working group was coordinated by Josse R. Thomas.

Appendix 2: List of abbreviations

To be completed with new entries when needed

ACRP	Association of Clinical Research Professionals (now part of Healixia)
AZ	Algemeen Ziekenhuis
BAPU	Belgian Association of Phase 1 Units (now part of Healixia)
BAREC	Belgian Association of Research Ethics Committees
CHIM	Controlled Human Infection Model (studies)
CTA	Clinical Trial Application
CTD	EU Clinical Trials Directive
CTEG	EU Clinical Trials Expert Group
CTFG	EU Clinical Trials Facilitation and Coordination Group
CTR	EU Clinical Trials Regulation
CU	Centre Universitaire
EC	(Human Research) Ethics Committee
EMA	European Medicines Agency
EU	European Union
EUR	Euro
FAMPH	(Belgian) Federal Agency for Medicines and Health products
FDA	US Food and Drug Administration
FPS	(Belgian) Federal Public Service
GBP	British pound sterling
GDPR	EU General Data Protection Regulation
IAF	Informed Assent Form
ICF	Informed Consent Form
ICH	International Council for Harmonisation for technical requirements for pharmaceuticals for human use
IRB	Institutional Review Board
IVDR	EU In Vitro Diagnostic Medical Devices Regulation
MDR	EU Medical Devices Regulation
MHRA	UK Medicines and Healthcare products Regulatory Agency
NMW	National Minimum Wage
OHRP	US Office for Human Research Protections
PWID	Persons Who Inject Drugs
REC	Research Ethics Committee
SOC	Standard Of Care
SWP	Safety Working Party (within EMA)
UK	United Kingdom
US(A)	United States (of America)
UZ(A)	Universitair Ziekenhuis (Antwerpen)
WG	Working Group (on Compensation)
WOCBP	Woman Of ChildBearing Potential

Appendix 3: More detailed background information

3.1. Ethics of compensation

Compensating subjects for their participation in clinical research is currently still to some extent a controversial ethical issue, as reflected in the international literature on this topic *(well summarised by Gelinas et al., 2018)* and the diversity in practice as seen also in Belgium (cfr section 3.2. of this Appendix).
Here, we briefly summarise the most debated ethical considerations. For more detailed information, the reader is referred to the specialised literature on this topic.
In section 6. and 7.1. of this Guidance, we present our consensus view on these considerations that served as the basis for the recommendations made in this Guidance.

To compensate or not (at all)?
Traditionally, participation in clinical research has largely been seen as altruistic. In this view, if subjects are well informed about the risks and benefits of a clinical study, they consent to participate out of free will 'for the greater benefit to society', and should not necessarily be compensated.
Over time, some forms of compensation became ethically acceptable, but still with different degrees of support and implementation. Thus, at one end, reimbursement of study/research-related expenses is currently widely accepted and implemented, while, at the other end, 'paying' subjects as an incentive to participate remains highly debated.

Risk of undue influence
Some forms of compensation to clinical research subjects, especially incentives to participate, can be potentially problematic because of the risk of their undue influence on the subjects free will to participate.
Today, this risk is considered by experts as grossly overrated. The well-intended anxiety of the past has a poor evidence base and is rated as overly paternalistic. Well-informed competent adults, either as participants or as representatives of vulnerable participants, seem perfectly fit to judge for themselves.
In the end, the crux is to strike a balance between fair compensation (showing respect to research participants) and overcompensation (undermining the validity of free informed consent).

Patient versus healthy volunteer
Compensating healthy volunteers for their participation in interventional clinical research, especially in non-therapeutic phase 1 studies, is widely considered as ethically non-problematic. On top of reimbursing their study-related expenses, it is generally accepted that they are also compensated for time investment and inconvenience. In practice this is also widely implemented as such.
In contrast and in practice, there is less consensus on compensating patients. At one end, some agree to compensate patients participating in (phase 1) studies without therapeutic benefit the same way as healthy volunteers. At the other end, some sponsors, especially academic or not-for-profit funders, consider it apparently ethically non-problematic not to compensate patients for their participation in clinical research, or even not to reimburse or compensate patients for their study-related expenses, reasoning that they are usually in (high) demand of care or (highly) willing to freely contribute to the advancement of science and the search for new treatment options.

Academic versus commercial research

In practice, most commercial sponsors agree to offer fair compensation to clinical research participants. Sometimes the evaluating EC has to hold them back when they tend to propose too high incentives for recruitment or for keeping participants in the study.
Academic sponsors or not-for-profit clinical research funders are usually less willing to compensate participants, especially patients (cfr previous paragraph). Some argue that their study budget is limited, leaving no room to compensate participants, although the cost of this budget item is usually modest. Let us hope that the current trend to more widely acceptance of fair compensation of research participants will encourage not-for-profit funders to integrate these costs into their study budgets.

3.2. Available guidance

Regulatory guidance on this topic is overall rather scarce and mostly general in nature. Here we limit ourselves to legislation and additional guidance applicable in the European Union (EU), and thus also in Belgium.

In the EU Clinical Trials Directive or CTD (Official Journal, 2001), there is a provision for vulnerable participants, such as minors, incapacitated adults, and participants in emergency situations, i.e. 'no incentives or financial inducements are given, except compensation'. Compensation in this document has been interpreted as compensation for travel costs, loss of earnings, pain, discomfort, etc. . In practice, this provision has been extended to other adult participants. In Belgium, the CTD text has been transposed as such in the Belgian Law concerning Experiments on the Human Person (Moniteur Belge, 2004).

In the more recent EU Clinical Trials Regulation or CTR (Official Journal of the EU, 2014), and the corresponding Belgian Law (Moniteur Belge, 2017), there is a general provision as follows: '*No undue influence, including that of financial nature, is exerted on subjects to participate in the clinical trial*'. The EU Clinical Trials Expert Group (CTEG) developed 'Part II Document Harmonisation Guidance' (Eudralex, 2020/1) with additional information on 'Compensation of trial participants'. Examples of acceptable compensation for trial participation include travel, accommodation and meal costs, loss of earnings, discomfort and suffering. In addition, some provisions are mentioned for financial incentives and conditional compensation in order to be acceptable. As follow-up to this document, the CTEG also developed a template 'Compensation for trial participants' (Eudralex, 2020/2) that may be used by sponsors as part of the Clinical Trial Application (CTA) dossier. It is also mentioned that this template is as well relevant for clinical trials that still fall under the CTD.
For vulnerable participants, such as minors, incapacitated adults, their legal representative, pregnant and breastfeeding women, the CTR is somewhat more explicit: 'No incentives or financial inducements are given to the subjects or their legally designed representatives, except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial'. In the Q&A document on the CTR (Eudralex, 2022) under Question 9.1 What is meant by 'compensation for participation', similar examples of acceptable expenses are mentioned, such as travel costs and costs for accommodation of the subject (+ the legal representative or accompanying person). In addition, a small token of appreciation is not considered an incentive.
Similar provisions can be found in the EU Medical Devices Regulation or MDR (Official Journal of the EU, 2017), the EU In Vitro Diagnostic Medical Devices Regulation or IVDR (Official Journal of the EU, 2017), and the corresponding Belgian Laws (Moniteur Belge, 2020 and 2022).

In all the aforementioned cases, the Regulations and Laws add that it is the assessing Ethics Committee that should agree on the appropriateness of providing compensation to research participants, as well as on the amounts and arrangements proposed. Therefore, one would expect ECs to issue more detailed guidance for stakeholders. Unfortunately, there are not many guidance documents from European or Belgian ECs publicly available.

Other more or less detailed position papers or guidance documents are available via internet, especially from the Anglo-Saxon world, e.g. from regulators outside the EU (such as FDA and MHRA), from RECs or IRBs, from research institutions or organisations, from pharmaceutical companies, and from other organisations. It would lead us too far to mention them all here, and they can easily be found using internet search engines. Some of them were consulted during the making of this guidance, mainly to check its completeness.

3.3. Situation in Belgium

The practice of compensating subjects for their participation in clinical research in Belgium is very diverse, and in that sense not very different from most other countries.

In 2017 some research on this topic was done by a student in the Master of Drug Development at the Faculty of Pharmaceutical Sciences at KU Leuven (Belgium), in the context of her master thesis (Maris, 2018). She did a literature study, investigated the practice of compensation in 231 clinical trials approved by the REC UZ/KU Leuven during 1 year (Oct 2016-Sep 2017), and interviewed 35 representatives from the different stakeholders involved in Belgium. From the results it was concluded that:
- The international ethical thinking was shifting towards a more fair practice of compensation.
- The practice in Belgium showed a great deal of variety, even within one single research institution.
- A majority of stakeholders agreed that some practical guidance would be welcome, in order to promote more clarity, transparency and harmonisation.

Although these results were presented to a wider audience of interest in Belgium during 2018 (to the members of RECs, at a BAREC and a BAPU symposium, and at an ACRP conference), unfortunately no common initiative to draft guidance was taken. As a result, over the next years, a few university hospital ECs drafted some guidance that is only applicable to clinical research projects submitted to their own EC. Therefore, it is expected that the practice of compensating research participants in Belgium today, although it may have evolved somewhat, is likely still very diverse and could still benefit from some harmonisation, and therefore from more practical guidance on the topic.

In the meantime, two other events occurred that make harmonised recommendations even more compelling in Belgium:

1°/ The implementation of the EU CTR, MDR and IVDR, with their counterparts in Belgian Law stipulating that the assessing hospital EC should be independent of the participating investigation centre(s). In Belgium, all Ethics Committees currently recognised by the Ministry of Health to assess clinical research in humans, all operate within a hospital. For each individual application within the context of these laws, the independent assessing EC is appointed by the Clinical Trial College, a body established within the Federal Public Service Health, Food Chain Safety and Environment. As sponsors

will no longer be able to choose the evaluating EC, they will be confronted with more diversified attitudes, eventually leading to even more divergent practice.
2°/ The opening of Vaccinopolis in 2022, a 'Centre for Evaluation of Vaccination' as part of the University of Antwerp, where - amongst other research - Controlled Human Infection Model (CHIM) studies will be performed. In such studies, participants may receive fairly high amounts of compensation for their time investment during long quarantine periods. Each of these individual clinical trials may be assessed by a different EC, initially possibly with no or limited experience with these studies, thus potentially contributing to further divergence in practice.

At the BAREC symposium in November 2022, it was agreed that practical recommendations issued by BAREC would thus be more than welcome. Subsequently, the BAREC Board decided to install the Working Group Compensation with the remit to draft guidance widely supported by the member ECs, which resulted in the current document.

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