Hogan Lovells

# Compliance issues in the conduct of clinical trials in the EU

## Presentation and interactive case study

Thirteenth International Pharmaceutical and Medical Device Compliance Congress
Mini Summit 16: R&D and Clinical Trials Compliance Workgroup

10 April 2019

Presented by Elisabethann Wright and Alexander Roussanov, Hogan Lovells Brussels

# Overview

- The applicable regulations in the EU
- Financial arrangements related to conduct of clinical trials and clinical investigations
- Relationship with healthcare professionals (HCPs), patients and patient organisations
- Investigational medicinal products (IMPs) and investigational medical devices
- Compliance with data protection requirements
- Anti-bribery and public disclosure requirements
- Case study

# Regulations governing medicinal products

- Conduct of clinical trials of medicinal products in the EU is currently governed by:
  - Directive 2001/20/EC (Clinical Trial Directive);
  - Commission Directive 2005/28/EC (Good Clinical Practice Directive);
  - Commission Directive 2003/94/EC (Good Manufacturing Practice Directive);
  - ICH E6 Good Clinical Practice (GCP) Guideline;
  - Volume 10 "Guidelines for clinical trial" of EudraLex;
  - Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects".
- Regulation (EU) No 536/2014 (Clinical Trials Regulation):
  - not yet applicable;
  - May begin to apply in 2020.

# Regulations governing medical devices

- Conduct of clinical investigations of medical devices in the EU is currently governed by:
  - Directive 93/42/EEC (Medical Devices Directive);
  - Directive 90/385/EEC (Active Implantable Medical Devices Directive);
  - MEDDEV 2.7/1 rev.4 "Clinical evaluation: Guide for manufacturers and notified bodies"
  - EN ISO 14155:2011 "Clinical investigation of medical devices for human subjects – Good clinical practice"
  - Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects".
- Regulation (EU) 2017/745 (Medical Devices Regulation):
  - starts to apply on 26 May 2020.

# Regulations governing protection of data privacy

- The collection and processing of personal data for the purposes of the conduct of clinical trials/clinical investigations is governed by:
  - Regulation (EU) 2016/679 (GDPR);
  - National implementing rules adopted by the EU Member States.
- EDPB Opinion 3/2019 concerning the Q&A on the interplay between the Clinical Trials Regulation and the GDPR:
  - Meaning?
  - Implications?
- Public disclosure requirements imposed by the national laws of the individual EU Member States and industry codes of conduct
- Anti-bribery and corruption laws:
  - e.g. the UK Bribery Act 2010.

# Budgetary obligations

- A pre-defined budget must be established
- The budget should be reflected in the agreements with:
  - Principal Investigator;
  - Research institutions;
  - CRO;
  - Other service providers (e.g. testing laboratories, contract manufacturers for IMP, IT services suppliers, patient recruitment services suppliers).
- The budget must be based on the estimated fair market value of the service provided by HCP and healthcare institutions:
  - Determined on the basis of internal SOPs and fully documented.

# Agreements

- Clinical trials/clinical investigation agreements must also address:
  - the roles and obligations of the parties;
  - liability of the parties and related indemnifications;
  - ownership of the clinical data and inventions;
  - safety reporting;
  - audits and interactions with the competent authorities;
  - supply, handling and use of the IMP/investigational medical device;
  - GDPR compliance, including pseudonymisation and data processing agreements;
  - conflict of interest and required authorisations/approvals by the HCPs' employers;
  - protection of confidential information and publication of the results;
  - compliance with transparency and public disclosure requirements.

# Relationships with HCPs

- Sponsors' relationships with HCPs relate to:
  - protocol development consultancy and advisory services;
  - patient recruitment;
  - conduct of the clinical trial/clinical investigation (Principal Investigator, Study team);
  - presentation/publication of the results.
- Each interaction with HCPs must be covered by a dedicated written agreement
- Selection of HCPs must be based on their expertise, knowledge and experience in the relevant therapeutic field
- HCPs must obtain all approvals required by the applicable laws and/or professional rules before entering into the agreement with the Sponsor

# Payment of HCPs

- Payments for HCPs' services must:
  - reflect the related Fair Market Value of the services provided;
  - be made to the HCP employer's account or HCP's professional account;
  - be documented and reported in accordance with the applicable public disclosure and transparency requirements.
- How **not** to do it:
  - contract the services of the HCPs on the basis of an oral agreement or short agreement letter;
  - select HCPs on the basis of past, current or potential future business to be generated by the HCP;
  - make cash payments or bank transfers to HCP's personal account or third party account;
  - fail to ensure that the HCP has obtained all required employer's approvals for entering into the agreement;
  - fail to comply with the transparency and public disclosure requirements applicable to the payments made to the HCP.

# Relationships with patients and patient organisations

- Sponsors must not be involvement in patient recruitment:
  - compliance with GDPR requirements;
  - no promotion of the IMP/investigational medical device;
  - assessment of the risks related to the use of social media.
- No inducement for patients to enrol in the study
- No direct contact or interactions with the patients enrolled in the study
- Interactions with patient organisations:
  - May relate to advice concerning patients' experience with the disease and their treatment needs;
  - All interactions must be governed by a detailed agreement;
  - All payments must be based on Fair Market Value and disclosed in accordance with the applicable requirements;
  - No attempts should be made to undermine the independence of the patient organisation.

# Regulation of IMPs and investigational medicinal products

- IMPs must:
  - Comply with GMP requirements;
  - Be subject to a manufacturing/import licence;
  - Product specifications in the IMP dossier (IMPD).
- Investigational medical devices must comply with:
  - Must comply with all rule governing medical devices with the exception of the intended purpose of the clinical investigation
- Can a clinical trial be conducted with an IMP and a non-CE marked medical device (e.g. drug delivery system, companion diagnostic)?
  - how to ensure the safety of the patients?
  - how to ensure the reliability of the data generated in the study?

# Supply of IMPs and investigational medicinal product

- The supply of the IMPs/investigational medical devices must be reflected in the agreement with the research institution:
  - conditions of supply;
  - no transfer of ownership or related intellectual property rights;
  - requirements for secure storage, handling, return, destruction and disposing of the IMP/investigational medical device;
  - no reverse engineering of the IMP/investigational medical device;
  - use only in accordance with the Protocol;
  - liability for product defects and losses and damages caused by the actions of the Principal Investigator and/or the Study team;
  - ownership of intellectual property rights related to any inventions or improvements.

# General Data Protection Regulation (GDPR)

- On 25 May 2018 the GDPR replaced the Data Protection Directive.
- Regulation = directly applicable in all EU Member States without the need for national implementing measures.
- Among the changes introduced by GDPR :
  - applies to all companies processing the personal data of data subjects residing in the EU, regardless of the company's location;
  - Breaches of GDPR can lead to fines of up to 4% of annual global turnover or €20 Million (whichever is greater).
- Directly applicable … but national laws will still exist, notably to define additional provisions according to the opening clauses

## Restrictions on processing of personal health data?

- Article 9.1 GDPR
- "Processing of personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, or trade union membership, and the **processing of genetic data, biometric data for the purpose of uniquely identifying a natural person**, **data concerning health** or data concerning a natural person's sex life or sexual orientation **shall be prohibited**."

# Pseudonymised Data is Personal Data

- Personal health data processed in clinical investigations in the EU must be pseudonymised.
- Article 4(5) of the GDPR defines pseudonymisation as:

  *"the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person"*

  – these data would include coded data transferred to study sponsor, when the investigation site maintains the additional information by which the data can be attributed to specific study subjects;

  – pseudonymous data transferred to study sponsor within the conduct of an investigation are subject, therefore, to the data protection guarantees established in the GDPR.

# Provisions of GDPR concerning secondary processing (I)

- Recital 47 – no future processing if patient does not expect this
- Recital 50 – future processing permitted where there is a link to existing processing activities but depends on context of data collection, particularly:
  - patient expectations;
  - nature of the data;
  - nature of future processing;
  - must have appropriate provisions for data minimisation.
- Recital 61 and Article 13.3 – Controller must provide information concerning future processing prior to this processing activity

# Provisions of GDPR concerning secondary processing (II)

- Recital 156 and Article 89.1:
  - must first determine if irreversibly anonymised data may be used; and
  - EU Member States must provide appropriate safeguards.
- Article 5 – no future processing if this is incompatible with initial purpose
- Article 13.3 - "*Where the controller intends to* ***further process*** *the personal data for a purpose other than that for which the personal data were collected, the controller shall provide the data subject* ***prior to that further processing with information on that other purpose*** *and with any relevant further information as referred to in paragraph 2.*"

# Sharing and transfer of personal data out of EU

- The GDPR imposes restrictions on when and how personal data may be shared with third parties
- Companies must enter into **"data protection agreements or addendums"** when sharing or receiving personal data:
  - data processing agreements in case of a controller – processor relationship;
  - data sharing agreements for controller to controller or joint-controllers relationship.
- There are additional restrictions on transferring personal data from EU to a country outside of the EU unless this country is regarded by the European Commission as providing a sufficient level of protection for personal data
- Examples of mechanisms for the transfer of personal data to the US:
  - European Commission's Standard Contractual Clauses;
  - Privacy Shield;
  - Patient consent.

# Anti-bribery Laws

- Interactions with HCPs in relation to the conduct of clinical trials/clinical investigations in the EU are governed by various national laws including two laws with extraterritorial effect:
  - US Foreign Corrupt Practices Act (FCPA):
    - prohibits making—or offering to make—a corrupt payment to a foreign (i.e., non-US) government official for the purpose of securing an improper advantage or obtaining or retaining business for or with, or directing business to, any person.
  - UK Bribery Act 2010:
    - wider scope as compared to the FCPA:
      - applies to bribes offered or given to any person (not only governmental officials);
      - does not require a corrupt intent on the part of the briber;
      - agreement to receive or acceptance of a bribe is also an offence;
      - failure by a company to prevent a bribery is also an offence.

# Transparency and public disclosure

- The public disclosure requirements are imposed by:
  - the national laws of some EU Member States;
  - the EFPIA Code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals and healthcare organisations ("EFPIA Disclosure Code");
  - the Codes of Conduct adopted by the national associations of pharmaceutical industry.
- EFPIA members are required to disclose, among other elements:
  - payments for consultancy services made to HCPs and healthcare organisations, including payments related to the conduct of clinical trials.
- EFPIA members required to disclose the information on their website or on a common platform developed by the national industry associations or the competent authorities of the EU Member States on annual basis.

# Transparency requirements in Belgium

- The Belgian "Sunshine Law" imposes mandatory public disclosure of information concerning all pecuniary advantages or benefits in kind granted, directly or indirectly, in Belgium or elsewhere, to HCPs, Healthcare Organisations (HCOs) and Patient Associations based in Belgium. These include:
  - payments and reimbursement of expenses for services and consultancy provided by HCPs;
  - financial support to Patient Associations.
- Annual disclosures must be made at latest by 31 May of the following year (i.e. 31 May 2020, for the period of January to December 2019) on the platform "betransparent.be".

# Transparency requirements in France (I)

- France is one of the EU Member States that has adopted a specific "Sunshine Law" into its legislation
- Code de la santé publique (French Public Health Code), as amended in 2016 to increase transparency, and its implementing decrees provide that:
  - companies that either manufacture or market medicinal products or that provide services in relation to these products must disclose, in particular:
    - fees paid to HCPs or other stakeholders amounting to 10 euros or above, including payments related to the conduct of clinical trials;
    - information concerning agreements entered into with HCPs or other legal entities established in France.

# Transparency requirements in France (II)

- Pharmaceutical companies are required to disclose this information on a specific website established by the French Ministry of Health https://www.transparence.sante.gouv.fr/
- According to the extensive interpretation of PHC provided by the French Ministry of Health, companies that are subject to the transparency requirements provided in the PHC include pharmaceutical companies that, while they have no authorised medicinal products in France, are developing investigational medicinal products

# Transparency requirements in the UK

- Members of the ABPI are required to annually disclose information concerning payments for services provided by UK HCPs or UK patient organisations. This information should include:
  - the total amount of payments made to UK HCPs;
  - the total number of UK HCPs who received such payments;
  - aggregate payments made to individual patient organisations.

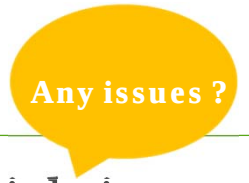
# Case study

Let’s practice!

# Case Study (I)


- GR8-MEDS is an international innovative pharmaceutical company, based in the US, engaged in the research and development of advanced therapy medicinal products for orphan diseases:
  - plans to conduct multiple clinical trials in the EU Member States, including the UK;
  - IMP will be manufactured in China and imported in the EU through a partner company established in Switzerland;
  - IMP will be administered to patients using an innovative drug delivery system that is manufactured and supplied in the US by partner company as “Research Use Only”;
  - GR8-MEDS intends to supply the drug delivery system to the clinical trial sites for a price that reflects the cost of the manufacturing and importing of the medical device;
  - anticipating possible opposition by the clinical trial site, GR8-MEDS hired a Key Opinion Leader to educate the clinical trial sites on the advantages and benefits of the use of the drug delivery system.

# Case Study (II)




- GR8-MEDS is in contact with a number of potential clinical trial sites:
  - investigating the ability of the sites to conduct the clinical trials;
  - collecting proposals for estimated budgets for the conduct of the clinical trial;
  - discussing the further roles of the potential clinical trial sites in:
    - recruiting patients;
    - encouraging other sites to participate; and
    - improving awareness of GR8-MEDS and their products within the medical community and public institutions.
  - discussing the key elements of the clinical trial agreements:
    - short, simple and focussed agreements;
    - not exceeding 7 pages, including annexes;
    - flexible payments provisions based on the performance of the clinical trial sites' in the conduct of the clinical trial.

# Case Study (III)


- GR8-MEDS is preparing the GR8-MA3X:
  - list of HCPs to be contacted by the company to provide services in relation to the conduct of the clinical trials:
    - protocol design advice;
    - patient recruitment;
    - Principal Investigator and sub-investigator services;
    - public speaking and social medial campaigns presenting the clinical trial.
  - the selection of the HCPs is based on:
    - their experience and qualifications; and
    - proximity to strategic decision-makers and purchasers.
  - Fair Market Value for the services provided by the HCPs will be calculated on the basis of performance and delivery indicators.

# Case Study (IV)


- According to GR8-MEDS policies payments to HCPs would be made through:
  - bank transfer to the HCP's professional bank account;
- Following numerous requests by HCPs, GR8-MEDS also agrees exceptionally to make payments through cryptocurrency transfers to the HCPs' cryptocurrency wallets.
- All agreements with HCPs are subject to strict confidentiality:
  - HCPs are permitted to disclose the existence of the agreement to third parties, including employer, only with GR8-MEDS explicit written consent;
  - no other public disclosure of information concerning the agreement would be permitted.
- GR8-MEDS does not verify whether the HCPs has complied with all applicable requirements concerning conflict of interest and employer's prior approval

# Case Study (V)


- GR8-MEDS anticipates that the company will face challenges in recruiting enough patients for their clinical trials in the EU targeting a rare disease
- In anticipation, GR8-MEDS plans for various patient recruitment activities:
  - public transport and newspaper advertising, including adds on buses in major EU cities;
  - posters in healthcare institutions' waiting rooms;
  - social media campaigns, including innovative "meet patients like you" multi-party text, voice and video discussions concerning the disease and potential treatments.
- GR8-MEDS also plans to work on exclusive partnerships ("one organisation-one sponsor") with relevant patient organisations to raise awareness concerning the clinical trials and improve recruitment:
  - partnership payments made to the patient organisations will be based on recruitment milestones.

# Case Study (VI)


- GR8-MEDS developed custom-made software for the entering, recording and analysing data generated in the clinical trials, including patients pseudonymised data
- The cloud based software is hosted on the US servers of GR8-MEDS and gives real-time access to the clinical trial data to all parties involved in the clinical trial, including sponsor and CRO
- GR8-MEDS received advise that the GDPR does not apply because:
  - GR8-MEDS are established in the US;
  - the cloud servers are based in the US;
  - pseudonymised data is not personal data;
  - GR8-MEDS, as a US-based sponsor of the clinical trials, is the owner of all clinical trial data, including clinical trial patients' personal data and biological samples and this data and samples are governed by US law.

Elisabethann Wright
Partner, Brussels
T +32 2 505 0926
ea.wright@hoganlovells.com

Alexander Roussanov
Counsel, Brussels
T +32 2 505 0931
alexander.roussanov@hoganlovells.com

Hogan Lovells

www.hoganlovells.com