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CTR, MDR AND GDPR – THE BIG BANG OF NEW EU REGULATIONS IMPACTING THE EU CLINICAL REGULATORY LANDSCAPE

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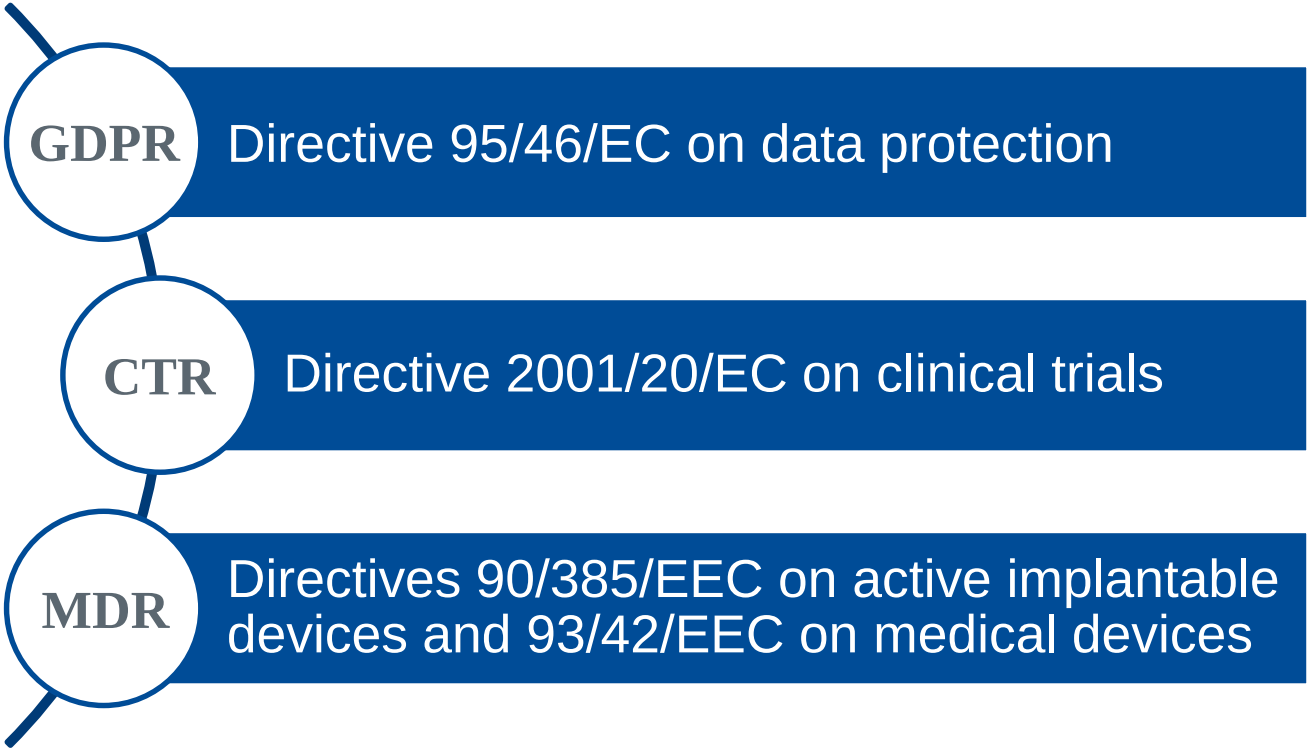
EU LEGISLATIVE DEVELOPMENTS

- Three new Regulations:
  - Regulation (EU) No 536/2014 of 16 April 2014 (CTR)
  - Regulation (EU) 2016/679 of 27 April 2016 (GDPR)
  - Regulation (EU) 2017/745 of 5 April 2017 (MDR)

GDPR, CTR, MDR: PREVIOUS DIRECTIVES



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GDPR, CTR, MDR: DATE OF APPLICATION

TIMELINE AND TRANSITIONAL PROVISIONS

TIMELINE FOR CTR APPLICATION

- Adopted on 16 April 2014
- Entered into force on 16 June 2014
- Will apply from 6 months after the publication of the Commission Notice that confirms that the EMA has verified through an independent audit that the EU Portal and EU Database are ready to go
- October 2017: EMA confirmed target to go live for second half of 2019
- June 2018: EMA informed that "*to account for EMA's relocation to Amsterdam, some further* ***planning adjustments*** *may be required…Adjustments for these events are not currently expected to have a major impact on overall timing for the project,* ***but will require careful management.***"

TRANSITIONAL PROVISIONS – 3 YEARS (ART. 98 CTR)

- Directive 2001/20/EC will be repealed on the day of entry into application of the CTR. It will however still apply three years from that day
  - YEAR 1: CT can be submitted under old or new rules
  - YEAR 2 AND 3: CT can be submitted only under CTR but trials authorized under Directive continue to be regulated by Directive (unless “switched”)
  - YEAR 4: ALL ongoing and new CT transitioned into CTR

TIMELINE FOR MDR AND GDPR

- Art. 120(11) MDR: Clinical investigations which have started to be conducted in accordance with the MDD and AIMD, prior to 26 May 2020, may continue to be conducted under those rules. However, from 26 May 2020 the reporting of serious adverse events and device deficiencies must be carried out in accordance with the MDR rules
- GDPR: no transitional rules **– it applies from 25 May 2018**

GUIDANCE ON SWITCHING A TRIAL FROM DIRECTIVE TO CTR

- Possibility open from day 1 of application of the CTR
- Only trials that comply with CTR as regards their “substantial requirements” can switch – responsibility of assessment rests with sponsor
- Not eligible:
  - halted trials
  - trials for which a substantial amendment is pending
- Trials that do not comply cannot switch unless a *request for substantial amendment* under CTR is filed and accepted
- Application to the EU Portal and Database, relying in principle on existing dossier + a consolidated protocol for multi-country trials reflecting common core provisions and national specificities as approved in each MS – if not sufficiently harmonized: request for substantial amendment
- Switched trials subject to all CTR requirements (e.g., transparency)

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GDPR, CTR, MDR: COMMON GROUNDS AND POTENTIAL TENSIONS

- GDPR promotes the protection of privacy and personal data in general
- Both the CTR and MDR refer to the need to protect the privacy of patients while promoting scientific development and advancement of new technologies
- Transparency and Innovation Vs. Privacy

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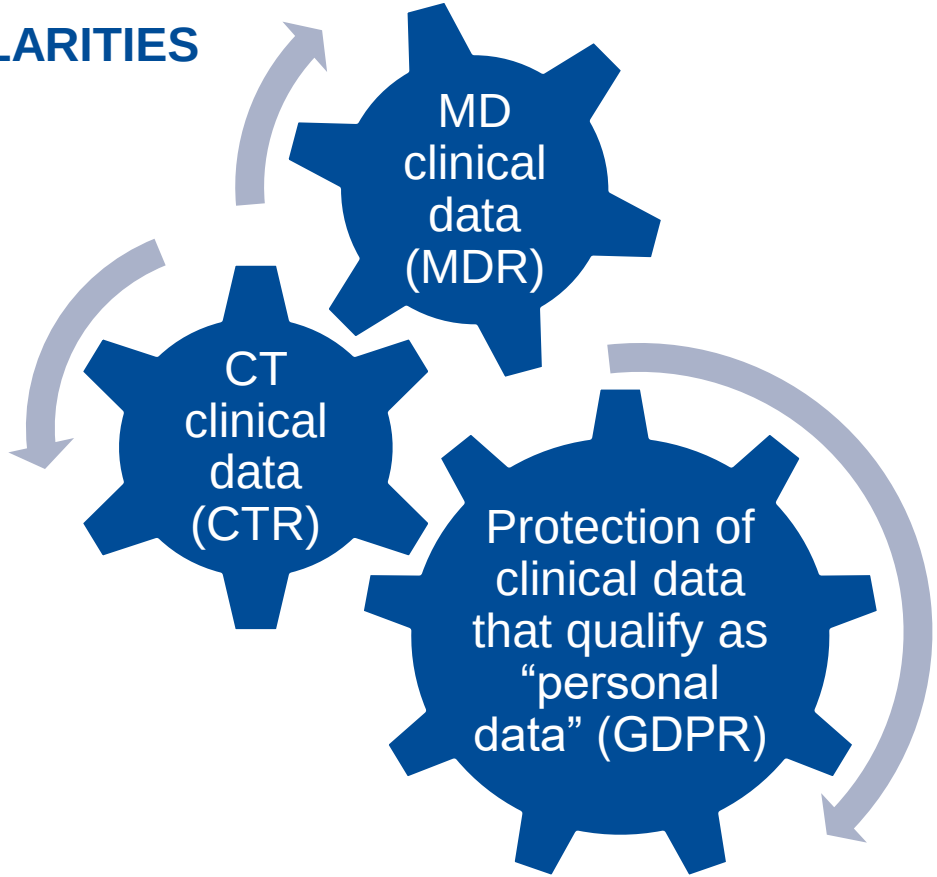
MDR/CTR SIMILARITIES



CTR, MDR: PARALLEL APPLICATION OF THE GDPR

- CTR → Data Protection (Art. 93): "*Member States shall apply Directive 95/46/EC to the processing of personal data carried out in the Member States pursuant to this Regulation*"

- MDR → Data Protection (Art. 110): *"Member States shall apply Directive 95/46/EC to the processing of personal data carried out in the Member States pursuant to this Regulation"*

CLINICAL INVESTIGATIONS (CI)

Applicable rules

- Article 15 + Annex 10 MDD Article 62 to 82 + Annex XV MDR
- MDR applies to clinical investigations concerning medical devices and accessories conducted in the EU (Art. 1)
- ISO 14155:2011 on good clinical practice and *most recent version* of Helsinki Declaration (Recital 64)
- MDR provisions on CIs largely aligned with those of the CTR

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Definitions	CTR (Art. 2)	MDR (Art. 2)
Protocol/Clinical investigation plan	*a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial*	*a document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation*
Investigational medicinal product/device	*a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial*	*a device that is assessed in a clinical investigation*
Sponsor	*an individual, company, institution or organisation which takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial*	*any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation*
Subject	*an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control*	*an individual who participates in a clinical investigation*

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Provisions	**CTR** (CT)	**MDR** (CI)
Informed consent (29 CTR/63 MDR)	✓	✓
Protection of personal data (93 CTR/110 MDR)	✓	✓
Incapacitated subjects (31 CTR/64 MDR)	✓	✓
Minors (32 CTR/65 MDR)	✓	✓
Pregnant or breastfeeding women (33 CTR/66 MDR)	✓	✓
Emergency situations (35 CTR/68 MDR)	✓	✓
Safety reporting (40-46 CTR/80 MDR)	✓	✓
Publication of results irrespective of outcome (37(4) CTR/77 MDR) subject to exceptions (81(4) CTR/73(3) MDR)	✓	✓
Scientific and ethical review by Ethics Committees (4 CTR/62 MDR)	✓	✓
One EU wide application for authorization (but MS opt out possible in MDR until May 2027) (5 CTR/78 MDR)	✓	✓
Corrective measures by Member States Authorities (77 CTR/76 MDR)	✓	✓
Legal representative of sponsor in the EU (for sponsors not established in the EU) (74 CTR/62(2) MDR): *responsible for ensuring compliance with sponsor's obligations*	✓	✓

One single EU-wide application for authorization	
CTR	**MDR**
In order to obtain an authorisation, the sponsor shall submit an application dossier to the intended Member States concerned through the portal referred to in Article 80 (the 'EU portal') (Art. 5)	The sponsor of a clinical investigation shall submit an application to the Member State(s) in which the clinical investigation is to be conducted (Art. 70)
	By means of the electronic system referred to in Article 73, the sponsor of a clinical investigation to be conducted in more than one Member State may submit, for the purpose of Article 70, a single application that, upon receipt, is transmitted electronically to all Member States in which the clinical investigation is to be conducted (Art. 78)
	The procedure set out in this Article shall, until 27 May 2027, be applied only by those of the Member States in which the clinical investigation is to be conducted which have agreed to apply it. After 27 May 2027, all Member States shall be required to apply that procedure (Art. 78)

PURPOSE OF CI IN MDR

- CTs are used to demonstrate the safety, quality and efficacy of new medicinal products. Similarly, CIs are used to establish the safety and performance of a new device (Art. 62)
- CIs ≠ Clinical evaluations of devices:
  - Art. 2(44) MDR: '**clinical evaluation**' means "*a systematic and planned process to continuously generate, collect, analyse and assess the **clinical data** pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer*"
  - Clinical evaluation is broader than clinical investigation
  - Clinical evaluation is compulsory for ALL medical devices ≠ CIs are mandatory for Class III and implantable devices, with certain exceptions (Art. 61(4))

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CLINICAL EVIDENCE VS. CLINICAL DATA

- **Clinical evidence** includes clinical data + clinical evaluation results
- **Clinical data** include information concerning safety or performance obtained from:
  - Clinical investigations of the device
  - Clinical investigations reported in scientific literature of an equivalent device
  - Reports published in peer reviewed scientific literature on other clinical experience of either the device in question or an equivalent device
  - Clinically relevant information from post-market surveillance

PUBLICATION OF DATA UNDER THE CTR

- All data and information submitted through the EU portal to be stored in the EU database
- Sponsor must publish a summary of the results of the CT (and a summary presented in terms understandable to a layperson) in the **EU database** irrespective of the outcome of the CT (Art. 37 (4))
- EU database must identify each clinical trial by a unique EU trial number
- ***No personal data of subjects can be publicly accessible (Art. 81(7))***

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PUBLICATION OF DATA UNDER THE MDR

- CI information will be published on **Eudamed** (Art. 73):
  - All applications or notifications for clinical investigations
  - Any exchange of information between the Member States and between the Member States and the Commission
  - A report and summary easily understandable to the intended user, by the sponsor, which include among others the results of the CI, irrespective of the outcome of the CI (Art. 77)
  - Reporting of serious adverse events and device deficiencies
- Eudamed will identify the CI by a Union-wide unique single identification number
- ***No personal data of subjects can be publicly available***

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INCREASED HARMONIZATION OF EVALUATION OF CLINICAL DATA: THE RECENT HTA REGULATION PROPOSAL

- The European Commission adopted on 31 January 2018 a proposal for a Regulation on health technology assessment ("HTA")
- Aims to increase cooperation on HTAs at EU level and to establish common rules for the clinical assessment part of HTAs, through:
  - Joint clinical assessments for (i) medicinal products subject to the centralized MA route (ii) certain high-risk medical devices and *in vitro* devices
  - Joint scientific consultations through which advice is given in the development phase to ensure robustness of clinical evidence in CTs and Cis

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IMPACT OF THE NEW EU DATA PROTECTION REGULATION

- EU General Data Protection Regulation ("GDPR") adopted on 14 April 2016 and entered into effect on 25 May 2018
- Specific legal obligations concerning the collection, processing and storing of data by "data controllers" (often the sponsor)
- "Data processors" also required to comply with the GDPR (i.e., any natural or legal person which processes personal data on behalf of the controller)
- GDPR Article 9(1)(j) - research exemption: special rules for processing of sensitive data (incl. health, biometric or genetic data) where the purpose is scientific research - including "privately funded research" (see Recital 159 GDPR)
- This is subject to compliance with appropriate safeguards, e.g., appropriate technical and organizational measures (to be implemented by processor also - GDPR Article 32)
- GDPR Recital 78: Security measures must meet the principles of data protection by design and default (e.g., minimizing the processing, pseudonymising and encrypting personal data)

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PROTECTION OF PERSONAL DATA UNDER THE GDPR

- **Personal data**: **"***any information relating to an identified or identifiable natural person***"**
  - **Data concerning health** (as sensitive data): "*personal data related to the physical or mental health of a natural person, including the provision of health care services, which reveal information about his or her health status*" (Art. 4(15)) This definition includes:
    - Medical data (e.g. medical examination reports, laboratory tests, information on a disease, medical history, etc.)
    - Administrative and financial data relating to health (e.g. social security number)
- Also new: definitions of **biometric data** and **genetic data**

HEALTH/BIOMETRIC/GENETIC DATA AS "SENSITIVE DATA"

- **Processing of "Sensitive Personal Data" is prohibited unless in some limited cases, e.g.:**
  - Data subject has given explicit consent (and unless national law prohibits such processing); or
  - Processing is required for purposes of:
    - Preventative or occupational medicine
    - Medical diagnosis
    - Provision of care or treatment
    - Management of healthcare services

    …where the data is processed by HCPs who are subject to professional secrecy under national law/rules of national competent bodies
- Processing is necessary for reasons of public interest in the area of public health (e.g., to ensure high standards of quality and safety of health care)

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CAVEAT – MS DISCRETION FOR HEALTH/GENETIC/BIOMETRIC DATA

- However, GDPR allows EU Member States to "*maintain or introduce further conditions, including limitations, with regard to the processing of genetic data, biometric data or data concerning health*"
- Consequences:
  - potential divergence of rules in EU Member States with different levels of stringency concerning the processing of health data
  - Controllers must comply with GDPR and any specific national provisions

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CONTROLLER AND PROCESSOR

- **Controller: "***the natural or legal person, public authority, agency or other body which, alone or jointly with others, determines the purposes and means of the processing of personal data*"
- **Processor: "***a natural or legal person, public authority, agency or other body which processes personal data on behalf of the controller"*
- In a clinical trial/investigation: many parties involved including Hospitals, Sponsors, CROs, vendors…
- Usually both sponsors and sites determine the purpose of the processing and therefore will be considered as *joint controllers* (Art. 26) under the GDPR
- CROs and vendors likely processors

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THE POSITION OF SERVICE PROVIDERS

- Controllers must use only processors which provide sufficient technical and organisaitonal measures to guarantee compliance with GDPR
- Agreement in writing (and mandated minimum content)
- New obligations for processors also as regards the appointment of sub-processors

KEY GDPR ISSUES AFFECTING CLINICAL TRIALS/INVESTIGATIONS

- Informed Consent
- Right to erasure
- Pseudonymisation/anonymization
- Special ruels on research
- Data transfers outside the EU
- DPO
- Privacy by design

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INFORMED CONSENT

- The subject gives consent (i) to participate in a CT or CI and (ii) to let the pharma or medical devices company and clinical center process his personal data
- In practice both are included in the informed consent form, however there has to be a distinction between the various processing activities
  - This is confirmed by Art. 7 GDPR: "*If the data subject's consent is given in the context of a written declaration which also concerns other matters, the request for consent shall be presented in a manner which is clearly distinguishable from the other matters, in an intelligible and easily accessible form, using clear and plain language*"

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INFORMED CONSENT TO PARTICIPATE IN A CT/CI (CLINICAL ASPECTS) (29 CTR/63 MDR)

- Consent must be in writing (or through appropriate alternative means when the subject is unable to write, i.e. audio, video etc.) dated and signed
- Specific consent provisions for vulnerable population
- Consent should be freely given and informed:
  - Nature, objectives, benefits, implications, risks and inconveniences of the CT/CI
  - Subject's rights
  - Conditions and duration of CT/CI
  - Damages compensation

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INFORMED CONSENT TO THE PROCESSING OF PERSONAL DATA (GDPR)

- Consent can be in writing (including by electronic means) or orally
- Consent should be given by a clear affirmative act (e.g. not silence or inactivity)
- Consent should be freely given, specific, unambiguous, and informed:
  - Identity of the controller, DPO and any recipients
  - The purpose for which data are processed
  - Any intention of the controller to transfer the data
  - The period for which data are stored
  - The rights of data subjects (access, rectification, erasure/right to be forgotten, prevent further processing, data portability…)

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RIGHT TO ERASURE

- All three Regulations:

Option to withdraw consent at any time without affecting the subject's position or the lawfulness of the processing based on the consent before the withdrawal

- **Right to erasure** or "right to be forgotten":

Does the subject have a right to erase all data collected when he withdraws consent from the CT or CI?

PSEUDONYMISATION/ANONYMIZATION

- Newly introduced definition under the GDPR of pseudonymisation: "*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*"
- Data protection applies to pseudonymised data, as they are considered information concerning an identifiable person (Recital (26))
- This provision applies to CTs and CIs where coded data are used
- ≠ anonymous data (i.e. data that cannot lead to the identification of the data subject) do not fall under the scope of the GDPR

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SPECIAL RULES ON RESEARCH

- The GDPR introduces special rules for scientific research
- What is "scientific research"?: Recital (159) GDPR : (…) "*For the purposes of this Regulation, the processing of personal data for scientific research purposes should be interpreted in a broad manner including for example technological development and demonstration, fundamental research, applied research and privately funded research* (…)"
- Does it include commercial research?
  - The Data Protection Directive already contained an exemption for research purposes, but this was generally interpreted to exclude commercial research
  - The broader language of the GDPR opens the door to the potential extension of the exemption to *commercial* research

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WHAT RULES FOR DATA IN SCIENTIFIC RESEARCH?

- Art. 89: No consent needed if processing is necessary for scientific research purpose based on Union or MS law which must be proportionate to the aim pursued, respect of the right to data protection and provide for suitable and specific measures to safeguard he rights and interests of the data subject (including data minimization, pseudonymisation, data security)
- Override a data subject's right to access, rectify and restrict processing as long as appropriate safeguards are implemented?
- Recital 33: sometimes not possible to identify a specific purpose at the time of collection in the framework of scientific research

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FURTHER PROCESSING/SECONDARY USE

- Recital 50: further processing for scientific research should be considered as compatible and lawful processing
- Article 5(1)(b) : further processing for scientific research should not be incompatible with the initial purposes if done in compliance with Art. 89
- Art. 6(4) lays down the criteria to check if a new processing purpose is compatible with the purpose for which consent was initially collected, namely: any link between purposes, the context/relationship between data subject and controller, the possible consequences of the further processing, the existence of appropriate safeguards
- Art. 89 describes specific safeguards (eg, pseudonymization)

WP 29 GUIDELINES ON CONSENT OF 28 NOVEMBER 2017

- Specific section on “Scientific Research”
- Notion of scientific research: narrow interpretation of research project set up in accordance with relevant *sector-related methodological and ethical standards*
- Call for restrictive interpretation to the exception to the obligation to specify a purpose (Recital 33)
- No exception to data subject rights (e.g. withdraw consent, right to erasure, right of access, etc.) if consent is the basis for legitimate processing: “*if a controller receives a withdrawal request, it should delete or anonymise the data straight away*”
- Calls for gap analysis/review of existing consents to ensure their compliance with GDPR: one-off exercise for transition to GDPR

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DATA TRANSFERS OUTSIDE THE EU

- How to legitimize transfers of personal data to recipients in “third countries”:
  - country of destination is covered by a so-called ‘adequacy decision’ adopted by the European Commission (e.g. New Zealand)
  - Transfer of data to the US: EU-US Privacy Shield agreement
  - EU Standard Contractual Clauses (“Model Clauses”)
  - Approved code of conduct, certification mechanism or “Binding Corporate Rules”

DATA PROTECTION OFFICER ("DPO")

- Independent and appointed in order to monitor compliance with the GDPR
- The appointment of a DPO is mandatory when: *"(…) the core activities of the controller or the processor consist of processing on a large scale of special categories of data pursuant to Article 9" (among others health data)*
- Article 29 WP guidelines on DPOs:
  - "Core activities" can be considered as the key operations necessary to achieve the controller's or processor's goals: e.g. *hospitals/health data*
  - "Large scale" is determined by the number of data subject concerned, the volume, geographical extent and duration of data processing, e.g. hospitals. Processing of patient data by individual HCP NOT "large scale"

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PRIVACY BY DESIGN

- GDPR: "*require data protection to be embedded within the entire life cycle of the technology*"
- Already at the time of the design of the means for collection of personal data, data controllers must implement appropriate organisational and technical measures (e.g. pseudonymisation) to comply with privacy rules
- By default, only personal data which are necessary for each specific purposes must be collected and retained
- Certifications/Codes of conduct may be used to attest compliance
- Documentation about risks and controls
- Technical measures (e.g. encryption, segregation, anonymization, pseudonymization)

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RECOMMENDED ACTIONS

- Consider procedures and wording used when obtaining consent/Conduct gap analysis of existing consents
- Ensure mechanisms are put in place to allow recording of withthdrawals of consent (and stop processing thereafter)
- Ensure internal processes exist to document the reasons underlying and the modalities for use of data for further (secondary) processing
- Review data subject access procedures and ensure coordination with service providers (eg CROs)
- Consider implications for IT systems used in the clinical setting: introduce privacy at design stage
- Select service providers based also on GDPR credentials/capabilities
- Review agreements with service providers: do gap analysis
- Consider appointing a DPO

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BREXIT CONSIDERATIONS

MHRA UPDATE ON BREXIT AND THE CTR

- The UK and EU reached agreement (Withdrawal Bill) on the terms of an implementation period [30 March 2019 until 31 December 2020]. During this time, the UK will no longer be an EU Member State, but EU rules and regulations will remain in place
- The CTR is expected to be implemented during 2020 and would therefore apply to the UK under the terms of the time-limited implementation period
- However, if the CTR does not come into force during the implementation period, the UK Government has confirmed that UK law will remain aligned with parts of the EU's CTR legislation that are "within the UK's control"
- The two key elements of the regulation that the UK would not be able to implement on its own after this time are the use of a shared central IT portal and participation in the single assessment model, both of which would require a negotiated UK/EU agreement regarding UK involvement following the end of the implementation period.

News story

Clinical Trials Regulation

Update on the Clinical Trials Regulation during the implementation period.

Published 6 August 2018
From: Medicines and Healthcare products Regulatory Agency

“In short, the Government are committing to being as aligned with the new EU clinical trials regulation as we possibly can be, subject to the negotiatory aspects…”

House of Lords (April 18, 2018), Baroness Goldie

“No matter what the outcome of negotiations, the UK is committed to offering a competitive service for clinical trial assessment”

MHRA

EUROPEAN COMMISSION
Directorate-General for Health and Food Safety

Brussels, 6 September 2018

NOTICE TO STAKEHOLDERS

WITHDRAWAL OF THE UNITED KINGDOM AND EU RULES IN THE FIELD OF CLINICAL TRIALS

The United Kingdom submitted on 29 March 2017 the notification of its intention to withdraw from the Union pursuant to Article 50 of the Treaty on European Union. This means that unless a ratified withdrawal agreement[1] establishes another date, all Union primary and secondary law will cease to apply to the United Kingdom from 30 March 2019, 00:00h (CET) ('the withdrawal date'). The United Kingdom will then become a 'third country'.[2]

Preparing for the withdrawal is not just a matter for EU and national authorities but also for private parties.

In view of the considerable uncertainties, in particular concerning the content of a possible withdrawal agreement, sponsors (both academic researchers and pharmaceutical companies) conducting or planning to conduct clinical trials, as well as investigators and other persons involved in the preparation and conduct of clinical trials in the EU are reminded of legal repercussions, which need to considered when the United Kingdom becomes a third country.

Subject to any transitional arrangement that may be contained in a possible withdrawal agreement, as of the withdrawal date, the EU rules on clinical trials, and in particular Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use[3] no longer apply to the United Kingdom. This has, in particular, the following consequences:[4]

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REGULATORY IMPLICATIONS

- As of March 30, 2019, depending on the results of the current negotiations, the UK will leave the EU (Brexit) and will thereafter be considered as a “third country”
- IMPs imported from UK will be subject to:
  - Importation authorization
  - The QP of the importer will have to ensure GMP compliance according to standards *at least equivalent* to EU standards, and that each batch has been checked in accordance with the CT authorization
- Need to appoint a legal representative
- No need to submit protocol-related or result-related information onto EudraCT (exceptions apply)

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GETTING READY

- Decide on cut-off date that works for your organization on *a study-by-study basis for CTR switch*
- Assess opportunities provided by co-sponsorship but be very diligent in documenting (in writing) the precise split of responsibilities
- Gap analysis of ICFs for compliance with CTR AND GDPR heightened requirements
- Monitor continuously guidance in the works
- Anticipate Brexit potential implications: e.g. need for EU rep.
- Adapt internal procedures for compliance, e.g.:
  - Need for robust internal quality audits of clinical trial documentation to address potential transparency challenges
  - Reassess content of CT submissions in light of heightened transparency

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CONCLUSION

- *More Regulations: more harmonisation/uniformisation*
- *Increased requirements for clinical evidence*
- *Common grounds/better coordination*
- *Beware of tensions between different regulatory goals and be prepared to reconcile*

QUESTIONS?

THANK YOU!

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