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COMMISSION STAFF WORKING DOCUMENT

**EXECUTIVE SUMMARY OF THE IMPACT ASSESSMENT REPORT ON THE
REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC**

Accompanying the document

**Proposal for a Regulation of the European Parliament and of the Council
on clinical trials on medicinal products for human use, and repealing Directive
2001/20/EC**

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1. PROBLEM DEFINITION

1. Clinical trials in the sense of the Clinical Trials Directive are investigations of medicines in humans where the medicines are applied outside normal clinical practice on the basis of a research protocol. Applications for marketing authorisation and publications in medical journals are based on data generated in clinical trials. Therefore, clinical trials are essential to develop medicinal products and improve medical treatment.
2. Clinical trials are regulated by the Clinical Trials Directive 2001/20/EC. The key aim of the Directive is to ensure safety and rights of subject, and reliability and robustness of data generated in a clinical trial.
3. The Clinical Trials Directive is criticised by all stakeholders (ranging from patients to researchers and industry) for having caused a significant decline in the attractiveness of patient-oriented research and related studies in the EU. Indeed, the number of clinical trials applied for in the EU has fallen from 5028 (2007) to 4400 in 2010. This trend greatly reduces Europe's competitiveness in the field of clinical research and, thus, has a negative impact on the development of new and innovative treatments and medicines. The main problems identified relate to the following issues:
4. Separate submission and diverging assessments and regulatory follow-up of applications for clinical trials: Clinical trials are subject to an authorisation (submission and assessment) and regulatory follow-up/supervision. The submission, assessment and regulatory follow-up for the *same* clinical trial are conducted in the different Member States completely separate from another. Moreover, within each Member State, two distinct bodies are involved: the national competent authority (NCA) and one or more Ethics Committee(s) (EC). This system induces elevated administrative burdens, and cumbersome hurdles to conduct research with associated delays of access to innovative, potentially life-saving, treatment.
5. Greater difficulties with conducting clinical trials due to regulatory requirements not adapted to practical considerations and needs: The risk to patient safety in a clinical trial can vary widely, depending on in particular the extent of knowledge and prior experience with the medicine which is object of the clinical trial (the 'investigational

medicinal product' - IMP). It is critical to take into account whether or not the IMP is already authorised in the EU or elsewhere. However, the Clinical Trials Directive does not sufficiently address these differences in risk and take them into account. Instead, the obligations and restrictions laid down in the Directive apply largely irrespectively of the risk to subject safety and without matching practical considerations and requirements.

6. Reliability of clinical trial data in a globalised research environment: There is a trend towards globalisation of clinical research, in particular towards emerging economies. Clinical research on a global scale is of benefit to the countries participating, to their populations and to global public health. However, the globalisation of clinical research poses a challenge when it comes to supervision of compliance with good clinical practice (GCP).

2. ANALYSIS OF SUBSIDIARITY

7. Union legislation on clinical trials is based on Article 114 of the Treaty on the Functioning of the European Union (TFEU). Based on Article 114 of the TFEU, the EU exercises a shared competence.
8. Harmonised rules open up the possibility of referring to the results and findings of clinical trials in applications for an authorisation for placing a medicinal product on the Union market. This is critically important as practically all larger clinical trials are often performed in more than one Member State. To address this issue, the Clinical Trials Directive lays down, at Union level, the exhaustive rules to be complied with for clinical trials.
9. While regulation of clinical trials is compatible with the principle of subsidiarity, there are limits set by the Treaties which have to be considered when formulating the policy options: The Treaty sets limits concerning the harmonisation of ethical aspects (i.e. in particular the need to obtain 'informed consent' from the subject). Moreover, there are several aspects which are of an intrinsically national nature, such as rules for establishing who is a 'legal representative' of a subject and rules on the liability for damages suffered by a subject.

3. OBJECTIVES

- **Objective No 1**: A modern regulatory framework for submission, assessment and regulatory follow-up of applications for clinical trials, taking into account the multinational research environment. This means the **operational objectives** of reducing administrative burdens and operational costs, and reducing delays for the launch of the clinical trial, as far as they are caused by regulation.
- **Objective No 2**: Regulatory requirements which are adapted to practical considerations, constraints and needs, without compromising the safety, well-being and rights of participants in clinical trials and without compromising data robustness. This means the **operational objectives** of reducing administrative burdens and operational costs as regards two key regulatory requirements: the annual safety report and the obligatory insurance/indemnification.

- **Objective No 3:** Addressing the global dimension of clinical trials when ensuring compliance with GCP. This means the **operational objective** of ensuring compliance with GCP of clinical trials conducted in non-EU countries.

4. POLICY OPTIONS

4.1. Objective No 1 — A modern regulatory framework for submission, assessment and regulatory follow-up of applications for clinical trials

4.1.1. *Policy option No 1/1 — No action at Union level and reliance on voluntary cooperation of Member States (baseline option)*

4.1.2. *Policy option No 1/2 — Single submission with separate assessment*

10. This policy option would consist of central submission, via an IT gateway located at EU-level, and subsequent separate assessment in each Member State concerned.

4.1.3. *Policy option No 1/3 — Single submission with joint assessment by Member States of issues not related to ethical aspects*

11. This policy option would consist of central submission and subsequent joint assessment by the Member States where the clinical trial takes place. Under this policy option the involvement of the Commission or the Agency (apart from the single submission point, see above) would be limited to technical support of the joint assessment, and to acting as 'facilitator' in the joint assessment.

4.1.4. *Policy option No 1/4 — Single submission with central assessment by the Agency of issues not related to ethical aspects*

12. This policy option would consist of central submission and subsequent central assessment by a scientific committee located and administered within the European Medicines Agency ('Agency').

13. In addition, each Member State concerned would issue a national decision covering the ethical aspects of the clinical trial.

4.1.5. *Policy option No 1/5 – Choice of legal form: adopting the text of the Clinical Trials Directive in the form of a Regulation*

4.1.6. *Policy option No 1/6 – Combination of policy option No 1/3 (joint assessment) and No 1/5 (legal form of a Regulation)*

4.2. Objective No 2 — Regulatory requirements adapted to practical considerations and needs

4.2.1. *Policy option No 2/1 — No action at Union level (baseline option)*

4.2.2. *Policy option No 2/2 — Enlarging the scope of non-interventional trials*

14. The Clinical Trials Directive applies only to 'interventional trials', but not to 'non-interventional' trials. Non-interventional trials are trials with authorised medicines, where subjects are not assigned in advance and where no additional intervention

takes place. This policy option would broaden the scope of non-interventional trials by removing the last requirement (additional intervention). Consequently, the scope of the Clinical Trials Directive would be narrowed.

4.2.3. *Policy option No 2/3 — Excluding ‘non-commercial sponsors’*

15. The requirements laid down by the Clinical Trials Directive are particularly onerous for sponsors who do not always have the means and resources to comply with them. This mainly applies to ‘non-commercial sponsors’. ‘Non-commercial sponsors’ are usually universities or academic institutes, foundations or charities. This policy option would follow the example of the U.S. and Japan by excluding ‘non-commercial sponsors’ from the scope of the regulation of clinical trials.

4.2.4. *Policy option No 2/4 — Removing regulatory requirements on the basis of the knowledge of the IMP*

16. This policy option would remove certain regulatory requirements (for example the compulsory insurance/indemnity and the obligatory annual safety report) for clinical trials with authorised medicinal products used for the authorised indication or with IMPs used in a well-known use.

4.2.5. *Policy option No 2/5 — Insurance/Optional ‘national indemnification mechanism’*

17. This policy option is relevant only for the issue of the obligatory insurance/indemnity. It would put Member States under an obligation to provide for an indemnification mechanism for clinical trials performed on their territory, taking account of the national legal system for liability. It would be optional for sponsors to join this national indemnification mechanism.

4.2.6. *Policy option No 2/6 – Combination of policy option No 2/4 and No 2/5*

18. This policy option is only relevant as far as the obligatory insurance/indemnification is concerned: Low-risk clinical trials would be excluded from the obligatory insurance/indemnification (policy option No 2/4). Other clinical trials would be covered by the obligatory indemnification mechanism (policy option No 2/5).

4.3. **Objective No 3 — Addressing the global dimension of clinical trials when ensuring compliance with GCP**

4.3.1. *Policy option No 3/1: Leaving the situation as it is (baseline option)*

19. The ‘self-regulation’ option would mean continuing to rely on voluntary commitment on the part of sponsors to ensure that clinical trials in non-EU countries are performed in accordance with GCP, regulatory supervision and inspections by non-EU countries in their jurisdictions, and some inspections by the inspectors of Member States in the framework of applications for marketing authorisation.

4.3.2. *Policy option No 3/2: Facilitating GCP inspections by increasing transparency*

20. This option would put sponsors under an obligation to register publicly all clinical trials whose results are used subsequently in an application for authorisation of a clinical trial or for marketing authorisation for a medicinal product. This would allow

enforcement authorities to intervene and police these clinical trials. It would also build up pressure for sponsors to comply with GCP.

4.3.3. *Policy option No 3/3: Inspections of non-EU countries' regulatory systems for clinical trial*

21. This option introduces the possibility for the Commission or the Agency to conduct 'system inspections' in non-EU countries, in order to assess whether their regulatory and enforcement system for clinical trials is equivalent to that in the EU.

4.3.4. *Policy option No 3/4: GCP inspections by the Agency in non-EU countries*

22. Under this option the Agency or Commission would be empowered to performing inspections in clinical trial sites in non-EU countries without drawing on inspection capacity provided voluntarily by Member States.

4.3.5. *Policy option No 3/5: Combination of policy option No 3/2 and No 3/3*

5. ASSESSMENT OF IMPACTS

5.1. Objective No 1 — A modern regulatory framework for submission, assessment and regulatory follow-up of applications for clinical trials

5.1.1. *Policy option No 1/1: No action at Union level and reliance on voluntary cooperation of Member States (baseline option)*

23. In terms of social/health impacts, the current 'patchwork' of separate assessment procedures for clinical trials by each Member State concerned does not necessarily ensure the highest possible standard of assessment in the EU. Moreover, the same clinical trial may be subject to different changes and adjustments in the authorisation procedure. These divergences can have an impact on data generated in the trial. If the conduct and design of the trial diverge too much, sponsors decide to withdraw the clinical trial from one or more Member States. This means that patients in those Member States are deprived of the potential benefits of clinical research, which leads to inequalities in public health.

24. In terms of economic impact the Clinical Trials Directive creates administrative costs of approximately 306m EUR per year and operational non-administrative costs of approximately 2 200m EUR per year.

5.1.2. *Policy option No 1/2 — Single submission with separate assessment*

25. As regards the impact on terms of health and patient safety there would be no change compared with the present situation.

26. In terms of economic impact this policy option would reduce administrative costs to 45.5m EUR. In terms of operational costs, however, the situation would be identical to policy option No 1/1, as this policy option is limited to an IT-tool to submit information. In terms of implementation costs, the one-off costs for IT and to running costs vary depending on the technical solution and range between 1.62m EUR and 6.3m EUR one-off costs, plus running costs between 0.34m EUR (plus 0.25 FTE)

and 1.26m EUR (plus 19 FTEs). The choice as to which technical solution is to be pursued is intrinsically linked to the decision as to where the single submission point is located at the Agency or at the Commission. This is a political decision to be taken at a later stage, to which the impact assessment serves as aid.

5.1.3. Policy option No 1/3 — Single submission with joint assessment by Member States of issues not related to ethical aspects

27. In terms of social/health impact, the protection and the safety and rights of participants would improve as compared with the baseline option, as expertise of different Member States would be brought together. A uniform response to the request for conducting a clinical trial would allow quicker start of a clinical trial on the basis of an identical protocol, thus removing the inequalities identified in the baseline option.

28. In terms of economic impact, this policy option would have largely the same impact as No 1/2. It would reduce administrative costs to 34.3m EUR, a saving of 271.7m EUR per year compared with the baseline option. In terms of operational costs, this policy option would lower the costs for performing clinical trials in the EU considerably (savings would be in the range of 440m EUR).

29. Depending on the extent of the support structure resource needs are between 1.5 and 7 FTEs. The choice as to the scale of the support structure is linked to the decision who provides the support structure: the Agency or at the Commission. This is a political decision to be taken at a later stage, to which the impact assessment serves as aid.

5.1.4. Policy option No 1/4: Single submission with central assessment by the Agency of issues not related to ethics

30. In terms of social/health impact, this policy option has the benefit of involving all Member States, thus assembling the best expertise of regulators available. However, this option might lead to additional delays in the start of a clinical trial because the dual approval system (national and EU level) is likely to lead to contradictions, hence creating additional delays in solving these. Moreover, the involvement of every Member State, including Member States not necessarily concerned, would add to the complexity of the discussions and of finding a compromise. In addition, this policy option would lead to an 'institutional continuum' between the authorisation procedure for clinical trials throughout development of a medicinal product and the marketing authorisation of the resultant product. This carries the risk of removing a 'fresh pair of eyes' that assesses the data at the end of the development process during the marketing authorisation application.

31. In terms of economic impact/costs, this policy option would lead to savings of 264.2m EUR in administrative costs. In terms of operational costs, the impact would be similar to policy option No 1/3, i.e. savings of approximately 440m EUR. In terms of implementation costs, these would relate largely to an additional role of the Agency. It can be estimated that the additional staff needs would be in the range of 4000 FTEs.

5.1.5. *Policy option No 1/5 — Choice of legal form — Adopting the text of the Clinical Trials Directive in the form of a Regulation*

32. This policy option would ensure that the Member States would base their assessment of an application for authorisation of a clinical trial on an identical text, rather than on various, inevitably diverging, national transposition measures.

5.1.6. *Policy option No 1/6 – Combination of policy option No 1/3 (joint assessment) and No 1/5 (legal form of a Regulation)*

33. In this policy option the joint assessment (pol. opt. No 1/3) would be strengthened by a legal text in the form of a Regulation (No 1/5). This would facilitate cooperation between Member States in the assessment of a clinical trial application.

5.2. Objective No 2 — Regulatory requirements adapted to practical considerations and needs

5.2.1. *Policy option No 2/1: No action at Union level (baseline option)*

34. The obligatory insurance/indemnity ensures that, in case of damages caused by a clinical trial, the subject receives compensation — irrespective of the financial means of the sponsor or investigator. The annual safety report can be a useful tool for NCAs or ECs to supervise and follow up the safety profile of an IMP, particularly if the compound is still largely unknown and not yet authorised.

35. The yearly costs for the obligatory insurance/indemnity and the safety report are approximately 222.8m EUR, plus administrative costs of 7.2m EUR. On the other hand, approximately 0.025% of all subjects successfully claim compensation for damages suffered in a clinical trial. Each damages claim is worth, on average, between 3 000 and 6 000 EUR.

5.2.2. *Policy option No 2/2 — Enlarging the scope of non-interventional studies*

36. In terms of social/health impact the immediate impact would be that these studies would be regulated at national level by Member States. Depending on the measures taken by each Member State, this would mean tighter, looser or no regulation of this type of study. In terms of economic impact/costs this policy option would generate savings of 16.98m EUR operational costs, plus 219 000 EUR administrative costs.

5.2.3. *Policy option No 2/3 — Excluding ‘non-commercial sponsors’*

37. In terms of social/health impact, subjects enrolled in a clinical trial run by an ‘non-commercial sponsor’ would not be protected at EU level. Nor would the EU rules ensuring the robustness and reliability of data apply. This would be a major drawback in terms of a creating a level playing field for conducting clinical trials in the EU without compromising on protection of rights and safety of patients in the EU and data robustness in the EU. This policy option would also have a negative impact on public health in general. Clinical trials run by ‘non-commercial sponsors’ can have a crucial impact on public health as the results may be published and, thus, impact to the choice of treatment options and treatment in general.

38. In terms of economic impact/costs this policy option would generate savings of 73.9m EUR operational costs, plus 926 000 EUR administrative costs.

5.2.4. *Policy option No 2/4: Removing regulatory requirements on the basis of the knowledge of the IMP*

39. Clinical trials with authorised medicinal products pose a risk to public health which is typically only minimally higher to that posed by standard care, if at all. Thus, removing the obligatory insurance/indemnity and the obligation to submit an annual safety reporting would have no discernible impact on subject protection. In particular, regarding insurance, if an (unlikely) damage occurs, there would be a number of additional types of insurance such as product liability insurance of the marketing authorisation holder for the authorised medicine, and professional negligence insurance by the treating physician.

40. In terms of economic impact/costs this policy option would generate savings of 34m EUR (operational costs) and 438 000 EUR administrative costs.

5.2.5. *Policy option No 2/5 —Insurance/optional ‘national indemnification mechanism’*

41. A national indemnification mechanism would give the same assurance of compensation for any subject suffering damages as the obligatory insurance/indemnity currently required by the Clinical Trials Directive.

42. Administrative and operational costs for sponsors would be limited and produce important savings compared to the baseline option. In terms of implementation costs, as the number of damage claims granted is very limited, costs for Member States would be limited to approximately 0.817m EUR per year.

5.2.6. *Policy option No 2/6 – Combination of policy option No 2/4 and No 2/5*

43. The impact in terms of public health and patient safety would be the sum of the policy options No 2/4 and No 2/5: Low-risk trials would be covered by other liability schemes (product liability etc.). Other than low-risk trials would be covered by the national indemnification scheme. In terms of economic impact/costs, the savings in this policy option would be 0.03m EUR higher than in policy option No 2/5.

5.3. Objective No 3: Addressing the global dimension of clinical trials when ensuring compliance with GCP

5.3.1. *Policy option No 3/1: Leaving the situation as it is (baseline option)*

44. This policy option would not address the questions raised in the problem definition.

5.3.2. *Policy option No 3/2: Facilitating GCP inspections by increasing transparency*

45. This policy option would contribute to securing compliance with GCP with the aid of a stronger degree of transparency. The economic impact/costs for sponsors will mainly be felt in the administrative costs (approximately 6.72m EUR per year) for submitting information on clinical trials in non-EU countries to a public register.

5.3.3. *Policy option No 3/3: Inspections of non-EU countries' regulatory systems for clinical trial*

46. This policy option would contribute to ensuring that clinical trial data referred to in EU marketing applications is reliable and robust. It would strengthen the general rule that clinical data from third countries has to stem from clinical trials which are based on principles equivalent to those in the EU.

47. In terms of economic impact/costs, the implementation costs are most relevant: they are at approximately 5 FTEs per year, plus costs of approximately 76 000 EUR.

5.3.4. *Policy option No 3/4: GCP inspections by the Agency in non-EU countries*

48. This policy option would contribute to securing compliance with GCP in clinical trials performed in a non-EU country. However, it would remain impossible to inspect all sites regularly and systematically. Moreover, inspections are usually conducted in the context of the marketing authorisation procedure, i.e. many years after the clinical trial has ended.

49. Resource needs at EU level would be approximately 1 300 FTEs.

5.3.5. *Policy option No 3/5: Combination of policy option No 3/2 and No 3/3*

50. This combination of policy options would further strengthen the impact of the policy options taken individually: the transparency (policy option no 3/2) allows better targeting inspections of non-EU countries' regulatory systems.

6. COMPARISON OF OPTIONS

6.1. Objective No 1 — A modern regulatory framework for submission, assessment and regulatory follow-up of applications for clinical trials

51. The baseline situation is insufficient to address the problem. While policy options No 1/2 (separate assessment), No 1/3 (joint MS assessment) and No 1/4 (assessment by the Agency) have one common element (the single submission point), they are mutually exclusive.

52. The common element which is part of policy options No 1/2, No 1/3 and No 1/4 greatly reduces administrative costs and thus contributes to addressing the problem.

53. Policy option No 1/2, however does insufficiently address issues of separate assessments of identical issues in relation to the same clinical trial. In this respect, policy options No 1/3 and 1/4, which address not only the submission process, but also the assessment process of a clinical trial application, are to be favoured. When comparing policy options No 1/3 and No 1/4, it results that policy option No 1/4 sets up a very heavy system which is prone for delays. It involves every Member State, which is not necessary in view of the roll-out of clinical trials. Only approximately 6 % of all clinical trials are rolled out in eight Member States or more. Considering this it seems disproportionate to involve every Member State in the assessment of clinical trial application. Added to this the dual approval (EU and national) stemming from policy option No 1/4 adds new complexities which would be avoided in No 1/3.

54. Policy option No 1/3 provides a ‘slimmer’ procedure than policy option No 1/4. For the initial authorisation it involves only the Member States where the clinical trial is to be performed (a mechanism would have to be set up to allow roll-out to additional Member States subsequently). Under policy option No 1/3 approval is also likely to be cheaper and faster than in No 1/4. This is in particular of interest for academic research and SMEs.
55. Policy option No 1/5 (Regulation vs. Directive) is not an alternative but an add-on. It would ensure an approach in assessment of a clinical trial and follow-up action, based on identical criteria.
56. Policy option No 1/6 is a combination of policy options No 1/3 and 1/5. It contributes further to achieving the objective No 1 by providing an identical legal framework for authorisation of clinical trials, thus facilitating cooperation between Member States as foreseen under policy option No 1/3. This helps to achieve the operational objectives of reducing in particular administrative burdens and delays.

6.2. Objective No 2 — Regulatory requirements adapted to practical considerations and needs

57. The baseline does not address the problem identified. Options No 2/2 (enlargement of the scope of non-interventional trials) and No 2/3 (exclusion of "non-commercial sponsors") have the effect of ‘shifting back’ regulation to Member States. In addition, regarding policy option No 2/3 it is difficult to see why rules designed to protect the safety and rights of participants and the reliability and robustness of data should apply to some types of sponsors but not to others.
58. Policy option No 2/4 (removing requirements on the basis of the knowledge on the IMP) brings about less savings for sponsors than policy option No 2/3. However, in terms of public health and patient safety it is superior to policy option No 2/3 as it leaves aside any differentiation between ‘non-commercial’ and industry sponsors and focuses on an objective criterion: the authorisation status of the IMP.
59. Policy option No 2/5 (national indemnification mechanism) can be a useful, cost-effective tool to address the specific issue of obligatory insurance/indemnity.
60. Policy option No 2/6 is a combination of policy option No 2/4 and 2/5. The combination reduces administrative burdens beyond policy option No 2/5 without compromising on patient safety.

6.3. Objective No 3: Addressing the global dimension of clinical trials when ensuring compliance with GCP

61. The baseline option is not satisfactory. Policy options No 3/3 (Inspections of non-EU countries' regulatory systems for clinical trial) and No 3/4 (GCP inspections by the Agency in non-EU countries) have relatively similar effects in terms of achieving the objective, even though the approach is different. Their impact diverges considerably as regards the impact on resources at EU level. Regarding policy option No 3/4, the budgetary constraints do not allow, at present, an increase in inspection activity in line with policy option No 3/4. The assessment of the impact of policy option No 3/3

shows that much can be achieved with far fewer resources than specified in policy option No 3/4.

62. Policy option No 3/2 (obligation of registration of all clinical trials) can make a useful contribution to effective control over clinical trials performed in non-EU countries. The burden for the sponsor, which is limited to administrative costs, is acceptable in view of the benefits created by this policy option.
63. Policy option No 3/5 is a combination of policy option No 3/2 and No 3/4: This combination strengthens further the tools to verify and ensure compliance, as it allows more targeted system inspections.

7. PREFERRED CHOICE OF OPTIONS

64. Regarding objective No 1, the preferred choice of policy option is No 1/6, which allows for a fast approval without setting up a new, central bureaucracy. In addition, in this policy option the legal form of a Regulation facilitates cooperation between Member States. Regarding objective No 2, the preferred policy option is No 2/6, which reduces costs (administrative burdens and operational costs) considerably without compromising on patient safety. Regarding objective No 3, the preferred policy option is no 3/5, which combines a resource-effective inspection of regulatory systems with a higher degree of transparency, in order to be able to target inspections.

8. MONITORING AND EVALUATION

65. A key indicator for achievements of the objectives is the number of clinical trials applied for in the EU, the number of multi-national clinical trials performed in the EU, the costs for clinical trials generated by legislation, and delays in launch of a clinical trial. This will be assessed by the Commission through regular reports from the EU-database on clinical trials, a public consultation and organisation and participation of *fora* where the legislation is evaluated by stakeholders.