Magyarországi
Klinikai
Vizsgálatszervezők
Társasága

An Expert Opinion of the Hungarian Clinical Trial Management Society on the public consultation paper issued by the European Commission on "ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC" c.

The EU CTD (Directive 2001/20/EC) became effective in 2004 with the aim to simplify and harmonize the administrative procedures connected with the clinical investigations performed within the EU as well as to continuously ensure

- the safety of subjects in clinical trials
- the ethical standard of the investigations conducted
- the reliability of the data emerging during trials

It is obvious that the Directive has increased the safety and confidence of the trials conducted in the EU but there are a lot of problems emerging from the implementation of the Directive, due to which EU has become less competitive in the field of clinical trials compared to other geographical regions.

Our opinion with regards to the specific topics of the discussion document is as follows:

Ad 1/

Directive has obviously brought advances with regard to uniformization of the approval process within EU and creates defense against denial of negative results via EudraCT and also the possibility of detecting non-professional (fraudulent, unethical) investigators. There are several countries, where the basis for the development of EU-conform local regulations has been pressed by the Directive, where the safety of the participants nowadays is more conform to the Directive (i.e. Bulgaria and in certain aspects also Romania). It is true even if in these countries the administrative difficulties and costs have simultaneously or - as a consequence - increased since then. The phenomenon detailed in the Preface of the discussion document the main point of which is the decreasing number of the clinical trials within EU is not exclusively due to the implementation of the Directive. In the background of this event is more likely the fact that time passed over the particular approval and reporting processes while countries outside EU had/have cost advantages. Despite all justified criticism the Directive has brought about many positive changes upon which it is possible and worth while building.

Ad 2/

The summary presented by the discussion document is correct. As far as it is obvious from domestic experience, specific EU authorities and ethics committees have different skills of decision-making and this causes constraint in the regional disposition of the trials or in the formulation of protocols, mainly due to the specific requirements of the authorities at the location of the intended registration. It does not rarely happen that in a specific trial – planned in different EU countries – where the applications have been submitted at different times in different countries the national authority or ethics committee raises questions which have been previously answered in another country thereby causing surplus administration and delay to both the authorities/ethics committees and the sponsors. This level of fragmentation brings EU into competition

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drawvback against regions of the same size (i.e. USA, India) as it is proven by the figures in the document.

Sponsors reckon with the possible slowliness, difficultness, inclaculableness and in many cases higher costs of the trials if EU countries are also involved.

There is one example of solution proposed during the preparation of the 2001/20/EC Directive (also presented in the draft documents) to issue one (1) EU CA and one (1) ethics opinion for a specific multinational clinical trial, with validity for the whole EU, and to have the personal and objective preconditions, specific local language documents judged by the local ethics committees of the country in question – within a strict, i.e. 15-day timeline or in a parallel way. Thereby the start-up period could be shortened significantly, the approval process within EU more apparent, cost effective and simpler.

There might be a variant of the above proposed system where in certain circumstances (i.e. trials with an investigational product registered within the EU, or late stage trials with registered products administered orally) the single EU approval/opinion became viable and the approval process of documents in local language could take place locally.

Another possible solution could be a system of „notification". EU authority issues the unique approval based on the opinion of the „central" EC and MS-s would have i.e. 15 days to reject the protocol in the MS in question – naturally after prior justification to the EU authority and the sponsor. The MS would possess the right to ask for additional information, also with prior justification to the EU authority and the sponsor.

Ad 3/

The evaluation of the state of affairs of the discussion document is correct. The increase in the administrative costs of approval procedure in Hungary is not as substantial as written in ithe document (or in the ICREL report) but the reason behind is more likely the fact that the Hungarian system was more bureaucratic even before the issue of the Directive. The evaluation/approval processes carried out parallely by different authorities are really diminishing the efficiency of the activity. The cost of the approval process is per capita really the highest in the EU, hence there is a judiciary fee in

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several countries. The several different country specific protocol versions also cause problems in many cases. The sponsors of clinical trials try to go in the direction of less resistance and lower costs. Therefore (as shown in the discussion document) Europe will be choosen for site of investigations only for specific reasons.

We are of the opinion that a unified operation of the national authorities can only be reached by declared regulation (see Ad 8.) In the new regulation the concurrencies of the Directive could be eliminated. Further problem is that the scope of tasks of ethics committees exceeds pure ethical questions. Several ethical committees perform so-called professional-ethics evaluation. Professional aspects should be transferred to the authorities (acknowledging that there are scientific-ethical problems which should further be evaluated by EC-s) similarly to the drug registration process which is exclusively the territory of the authorities. It would be logical that authorities should professionally supervise clinical trials which serve as basis of issuing the marketing authorization. There are also rationales for the uniformization and centralisation of the ethics procedures – there cannot be substantial differences in this field between European countries: what is unethical i.e. in Germany is unethical in Hungary, too.

Ad 4)

We think that option „b" – one single evaluation/approval for the territory of the EU is the more favourable alternative. The consultation of the different national authorities would certainly not speed up the process, however, the national specificities would be respected more satisfactorily. Establishment of a specific authority working on the basis of unified ethics principles specified by the MS-s would obviously need the partial transfer of the competence of national authorities (giving forth of this fact in local regulations) and such a board would not represent one MS's authority (with rotating task ordination among the countries) but different MS's candidates could comprise such a gremium. The hazard of such solution is that the evaluation standpoint system emerging from such a gremium may contain all the particular wishes of the MS-s, thereby making the operation impossible and may also increase the bureaucracy (which

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is opposite to the aim described). Specific problem is demostrated by the multilingual character of the EU (patient related documents in local language). One possible solution is the prompt submission of those documents (i.e. informed consent) by the central authority to the local authorities for evaluation and the result built in into the final approval (other proposals see also ad2) and ad 3)).

Ad 5)

The explanation of the discussion document does not explore why decentralization of ethics evaluation should remain at national level except for the single country trials. In this regard there is no difference between the MS-s which could establish different needs, „national specificities". Therefore also in our opinion the version described under 3.4.1 is feasible, with one single professional-ethics opinion throughout Europe also in a multinational clinical trial. Personal and objective preconditions, documents in local language could be evaluated at country level (EC), with a strict 15-day approval time or parallelly. In a „super committee" of the Union the MS-s should get representation, i.e. with a rotary chairmanship enabling MS-s getting similar representation in it. Thus the possible country specific differences would also be represented in the committee.

As written in the document the ethics opinion and the approval of the authority should remain clearly distincted and the concurrences and overlappings of the existing system should be minimized or eliminated. The typical territories of such a distinction are : the evaluation of the professional-scientific establishment of the protocol, the evaluation of the insurance and the scientific value of the Investigator `s Brochure.

In case this is not the possible way of solution the „one-stop-shop" is the better choice. A network of the EC-s of MS-s in our opinion would not speed up the processes and the effective exchange of information, therefore inefficient. The system of parallel evaluation would be a promising solution hence i.e. in Hungary the 2/3 of time spent for the approval process belongs to the EC.

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Ad 6)

The document describes the situation appropriately. Although GCP is not law a lot of people take GCP into account as the most important system of rule s with regard to clinical investigations. This is the cause of many misunderstandings, inconsistencies and overwhelming reports hence GCP does not contain uniform set of guidelines which could help transfer its – in many cases very complicated and hardly c oncretizable – `frame` instructions to rules to be followed in practice.

Sponsors try to do their best to comply with the presumed or real expectations which lead to necessarily sophisticated sponsor -specific procedures. As a paradox reaction, it increases the burden on the authority, hence people doing evaluation should get orientated in documents varying both in format and content . Only after this can they commence evaluating the content of applications. There is also a practice of overinsurance due to fear of rejection. The world of clinical investigations is very sophisticated therefore it is dubious w hether it is possible to elaborate a reporting system which a) can be obligatory for everyone regarding format and content and which b) covers all recent a nd future variances adequately.

The definition of „substantial amendment" in the Directive is hard to interpret. As referred to in the document confusions are caused and the different practice of the various MS-s results in over -compliance. It could easily be resolved during modification of the Directive.

Similarly to the substantial amendment the reporting of SAE and SUSAR is not unambiguous either. During the planned modificatin of the Directive attempts should be made to comply with the technical possib ilities of the 21st century and the real risks. It could also be raised that EU should initiate the modification, sophistication of the relevant parts (5.17.1) of ICH -GCP.

The question on non -interventional trials also deserves consideration - these should be withdrawn from the scope of the Directive. This would need first the definition of this category otherwise the recent situation does persist (here yes, there no), unless the approval process is centralized. The definition remains necessary even in th is case

hence the national trials presumably remain in local competence. We believe there is no necessity and indication to establish uniform rules for all clinical investigations hence specific ones will anytime need exception-making.

Also Phase I studies have specific properties – „monotonous" design, subjects get paid for participation, etc. – in case of extension of indication provided that the mode and dose of administration remain unchanged there is no surplus risk relative to the daily routine. Phase IV studies are also a specific world. It would be necessary to establish unique rules for trials not classifiable as to the usual clinical trial categories.

There might be a solution to establish specific fora for the evaluation and approval of these studies involving professionals with comprehensive knowledge, routine. In case of introduction of the formerly proposed unique EU approval process, the introduction of specific fora (Phase I, Phase IV, pediatric, etc.) would need less investment than the maintenance of some thousands of ECs.

Ad 7)

The description is correct. The recent system of SUSAR reporting increases the risk and brings no additional value. Unnecessary cost is generated at all participants (CAs, ECs, sponsors, investigational sites – like processing, storage, follow-up, etc.), thus resulting in increased price of the drugs. This surplus will finally be paid by patients in EU. Non-industry sponsors can hardly comply with these rules.

Ad 8)

There are pro-s and con-s to all proposals described in the document. Harmonisation can hardly be achieved via directives – different countries have adopted the content differently. Perhaps decrees could give a better guidance. This process has meanwhile started (see 1901/2006/EC decree (12.12.2006) of the EP and Council with regard to pediatric drugs. With respect to the fact the issuance of marketing authorizations is not a local task any more it is justified to increase the regulation level with respect to clinical

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investigations (which are the vestibules of the registration process) onto a decree level, too.

An advantage of the a Decree would undoubtedly be its direct effect on the legislation of the MS-s, there is no possibility for „interpretation" with reference to „national specificities". In the 21st century it is not easy to reveal national specificities that justify distinct national regulations, i.e. in the field of research ethics. Likewise, if a study is not acceptable in one country it should not be ethical in another. It is clear that this type of regulation will be very sophisticated and the compliance with it will require increased inspection activity. Equilibrium should be found among needs in the new regulation, the uniformity of the national laws and the possible maintenance of the level of administration (no increase!).

Ad 9)

There is a need for uniform system of evaluation and regulation in this respect, there is no room for exceptions. This leads to increased patient safety. Besides the system should be able to manage different types of trials which indicates different handling of Phase I and IV trials.

Ad 10)

If there is a movement in the direction of „one authority", in our opinion, the sponsor side should accomodate to it. It is hardly imaginable that among academic sites there is no competent entity which might be responsible for the consultations with CA.

Ad 11 & 12)

The question raised by discussion document is very compex. In case there is a unique Europeen process and system of fora there is less need for voluminous legislation hence the „soft law" produced by the fora is as obligatory as the laws themseves f. If no (or only particular, i.e. with regard to the activity of the authorities) centralization of the

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evaluation/approval process is decided a detailed elaboration of the decree mentioned afore (or at least a very comprehensive modification of the Directive) is necessary.

Ad 13)

We would not prefer the withdrawal of „academic" sponsors from the scope of the Directive. It could lead to potential hazard of several hidden „academic" studies the approval process of which would be less strict, the negative results could be easily neglected, the positive result could be easily admired and transferred to the official documentation. Our proposal is to ease the procedure of such investigations (some countries introduced such reliefs, i.e. Hungary)

Ad 14)

In our opinion the regulation for pediatric studies is more or less adequate, too. The wearisome widespread of these investigations is more likely due to personal and financial causes where legal regulation most probably would not make any changes. The number of pediatric studies should be increased, sponsors have to be motivated to perform such studies. A potential mode of action could be the minimization of the timelines of approval process for these studies. The only way of diminishing EU competition drawback is if the regulation process becomes more scientific-professional (less bureaucracy-oriented). This applies also to the so-called soft law.

Ad 15)

With respect to this situation the elaboration of a proper `accessory law` would be necessary. The recent „flexible" interpretation of rules is not a solution.

Ad 16)

In a publication of 2009, evaluatiing the 10-year (1997-2008) experiences of FDA inspections the results show substantial differences in the quality of data of clinical investigations at different geographical regions. The highest quality data originate from

Eastern Europe while Western Europe produces the worst data quality. The term „3rd country" used in the document covers very heterogenous group of countries which cannot be managed uniformly either with respect to enrolment speed or data quality, or the strictness of the ethical evaluation process of clinical investigations. The principle pointed out in the material (the compliance with international guidelines, principles and legislations of clinical investigations should be inspected more strictly) is subject to equivocal understanding from our side but not obviously in the EU vs. „3-rd country" context.

Ad 17)

Besides alternatives written in the discussion document there is the possibility of a certain „bar list". In the US there is a bar list of investigators/investigational sites, and EudraCT established its basis also within EU. There is also a possibility of establishing it in clinical trials in „3rd countries", retrospectively at the beginning. National authorities can also be encouraged to inspect more frequently the compliance with international standards. In the opposite case – like airline companies - EU could exclude data originating from specific countries from the acceptance process without extra evaluation. This could lead to motivation (and retarding force) to those countries. Naturally its prerequisite is not to interfere with international laws. The co-operation between authorities of ICH regions could also be increased (timing of inspections, exchange of information, common „bar list", common decision on exclusion, etc).