



Good clinical practice of medicinal products during the COVID-19 pandemic

ENGLISH VERSION 13 MAY 2020



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INTRODUCTION

Due to the current situation related to the spread of the SARS-CoV virus and the dynamic increase in COVID-19 incidence, the protection and safety of clinical trial participants become the highest and absolute priority.

According to the Statement of the President of the Office for Medicinal Products, Medical Devices and Biocidal Products (URPL) of 19 March 2020 regarding clinical trials conducted during the pandemic, investigators, sponsors and other persons/entities involved in conducting clinical trials are advised to introduce amendments arising from the need to adapt to the epidemiological situation and to consider them as urgent safety measures (in accordance with Article 37y of the Act of 6 September 2001 Pharmaceutical Law [PF]).

The industry organizations POLCRO (Polish Association of Clinical Research Organizations), GCPpl (Polish Association of Good Clinical Practice) and INFARMA (The Employers' Union of Innovative Pharmaceutical Companies) are of the opinion that the SARS-CoV-2 pandemic is a very serious event that affects the safety of clinical trial participants.

As a result, sponsors and investigators are required to consider all risks and take appropriate measures to ensure the safety of clinical trial participants.

Therefore, we provide suggested good practices and possible solutions that can be considered and adapted to each clinical trial (commercial and non-commercial) in order to minimize the risk. Some of the recommendations presented already exist as solutions introduced by sponsors, study sites or bioethics committees.

This document is intended for large-scale distribution and can be modified to reflect the latest recommendations, statements and comments from the URPL, the bioethics committees, the Ministry of Health, and other institutions and entities involved in conducting clinical trials.

At the same time, we would like to draw your attention to false information regarding recommendations related to COVID-19. We suggest using only proven sources, especially:

- <http://urpl.gov.pl/pl>
- <https://abm.gov.pl/>
- <https://www.gov.pl/web/zdrowie>

Please verify the emerging reports carefully and contact the persons mentioned in this document for confirmation (please see 5. CONTACT)

We would also like to thank all the persons and institutions that contributed to the drawing up of these recommendations, which will continue to be developed.

LIST OF RECOMMENDATIONS AND GUIDELINES

1. Information from the President of May 8, 2020 on the European Commission's guideline on the management of clinical trials during the SARS-CoV-2019 pandemic (COVID-19)
<http://urpl.gov.pl/pl/informacja-prezesa-z-dnia-08-maja-2020-r-w-sprawie-wytycznej-komisji-europejskiej-dotycz%C4%85cej>
2. Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic version 3, 28/04/2020.
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf
3. Information of the President of the Office of 20 April 2020 on updating information in medicinal product information in the field of reporting adverse reactions
<http://www.urpl.gov.pl/pl/informacja-prezesa-urz%C4%99du-z-dnia-20-kwietnia-2020-r-w-sprawie-aktualizacji-informacji-w-drukach-0>
4. Act of 16 April 2020 on specific support instruments in connection with the spread of the SARS-CoV-21 virus)
<http://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20200000695/T/D20200695L.pdf>
5. Statement of the Association of Members and Employees of Ethics Committees in Poland towards the actions of bioethics committees during epidemic state in Poland, 6 April 2020
https://nil.org.pl/uploaded_files/art_1586179919_stanowisko-stowarzyszenia-czlonkow-i-pracownikow-kb-w-zwiazku-z-epidemia-06-04-2020.pdf
6. Communication from the Director General of 3 April 2020 regarding the activities of the Office of the Office (URPL) during the SARS-CoV-2 epidemic
<http://urpl.gov.pl/pl/komunikat-dyrektora-generalnego-z-dnia-3-kwietnia-2020-r-w-sprawie-dzialalnosci-kancelarii-urzedu-0>
7. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic / Guidance for Industry, Investigators, and Institutional Review Boards updated 02 Apr
<https://www.fda.gov/media/136238/download>
8. ACT of 31 March 2020 amending the Act on special solutions related to the prevention, prevention and eradication of COVID-19, other infectious diseases and crisis situations caused by them, as well as certain other acts
<http://dziennikustaw.gov.pl/D2020000056801.pdf>
9. Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials (draft) 25/03/2020
https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical_en.pdf

10. Information from the President of the URPL of 24 March 2020 concerning the European Commission Guidance on the Management of Clinical Trials during the SARS-CoV-2019 Pandemic (COVID-19)

<http://www.urpl.gov.pl/pl/informacja-prezesa-z-dnia-24-marca-2020-rw-sprawie-wytycznej-komisji-europejskiej-dotycz%C4%85cej>

11. Statement of the President of the URPL of 23 March 2020 regarding update of information contained in the request for derogation from registration requirements provided for in Article 55(1) of Regulation No. 528/2012

<http://www.urpl.gov.pl/pl/komunikat-prezesa-z-dnia-23-marca-2020-roku-w-sprawie-aktualizacji-informacji-zawartych-we-wniosku>

12. Home visits during the COVID-19 outbreak of 23/03/2020

http://adst.mp.pl/s/www/covid19/wizyta+domowa_COVID19.pdf

13. Statement of the President of the URPL of 19 March 2020 on Clinical trials during the pandemic

<http://www.urpl.gov.pl/pl/komunikat-prezesa-z-dnia-19-marca-2020-rw-sprawie-badań-klinicznych-prowadzonych-w-warunkach>

14. Information from the President of the URPL of 19 March 2020 concerning the European Medicines Agency's call to pool research resources into clinical trials of medicinal products used in the treatment of SARS-CoV-2019 (COVID-19) infections

<http://www.urpl.gov.pl/pl/informacja-prezesa-z-dnia-19-marca-2020-rw-sprawie-komunikatu-europejskiej-agencji-lek%C3%B3w>

15. Communications from the Director General of the URPL of 17 March 2020 concerning the activities of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products relating to the SARS-CoV-2 pandemic

<http://www.urpl.gov.pl/pl/komunikat-dyrektora-generalnego-z-dnia-17-marca-2020-rw-sprawie-dzia%C5%82alno%C5%9Bci-urz%C4%99du-rejestracji>

16. Statement of the President of the URPL of 13 March 2020 on granting a derogation from the registration requirements provided for in Article 55(1) of Regulation 528/2012 regarding biocidal products in relation to the SARS-CoV-2 pandemic

<http://www.urpl.gov.pl/pl/komunikat-prezesa-z-dnia-13-marca-2020-rw-sprawie-udzielania-odst%C4%99pstwa-od-wymog%C3%B3w-rejestracyjnych>

17. Information of 13 March 2020 on measures to inhibit the spread of SARS-CoV-2019 virus

<http://www.urpl.gov.pl/pl/informacja-z-dnia-13-marca-2020-roku-w-sprawie-dzia%C5%82a%C5%84-zmierzaj%C4%85cych-do-zahamowania>

18. EFGCP-AWP Covid-19 Repository. Repository of publications for Clinical Trials in relation to COVID-19

<https://efgcp-events.eu/Clinical-Trials-COVID19-Repository.php>

1. REGULATIONS AND LEGAL ASPECTS

1.1 LEGAL SECURITY

1.1.1 Handwritten signature (wet-ink) - is there an alternative?

Currently, a qualified signature and a trusted signature are treated as equivalent to a handwritten signature.

1. Trusted signature:

<https://www.gov.pl/web/cyfryzacja/podpisz-dowolny-dokument-wykorzystaj-do-tego-profil-zaufany>

Every person with a trusted profile has a trusted signature; a trusted profile can be obtained free of charge. Documents can be signed via a "signer":

<https://moj.gov.pl/uslugi/signer/upload?xFormsAppName=SIGNER>

2. Qualified signature is a paid service. List of suppliers is provided below:

<https://www.nccert.pl/index.htm>

3. Signatures issued by qualified entities in the EU can also be used:

<https://www.biznes.gov.pl/pl/firma/sprawy-urzedowe/chce-zalatwic-sprawe-w-urzedzie/dlaczego-warto-zalatwiac-sprawy-urzedowe-przez-biznes-gov-pl-i-jak-to-zrobic/profil-zaufany-i-podpis-elektroniczny-zalatwianie-spraw-online-na-biznes-gov-pl-oraz-innych-serwisach-administracji>

A list of bodies issuing a qualified electronic signature in the EU is available at the following link:

<https://webgate.ec.europa.eu/tl-browser/#/>

4. Representatives of GCPpl, INFARMA and POLCRO shall jointly attempt to enter into dialogue with the President of the URPL, acting on behalf of the associated entities, in order to obtain information on whether the rules on submission of original documents bearing a wet-ink signature could be departed from or temporarily replaced with more flexible requirements during the pandemic. In our opinion, no specific solutions should be suggested to the President, but the President should only be convinced to verify which derogations the URPL could agree to. During the dialogue, it is worth pointing out to the President the shortcomings of the current solutions.

1.1.2 Article 37y of the Pharmaceutical Law - what does it allow us to do?

Article 37y allows to abstain from conducting a clinical trial in accordance with the applicable protocol if any event which is likely to affect the safety of the clinical trial participants occurs. The PF provision referred to above applies only to initiated and pending trials. The sponsor shall immediately inform the President of the URPL and the bioethics committee which has issued an opinion on the clinical trial about the above circumstances and the safety measures taken.

1. We recommend proceeding in accordance with the Communication of the President of the URPL of 19 March 2020 on clinical trials conducted during the pandemic, which recommends that amendments arising from the need to adapt to the epidemiological situation should be considered as urgent safety measures in accordance with Article 37y PF and provides that the above information can be sent by e-mail to the following address: urpl@urpl.gov.pl
2. We propose to use a similar approach in communication with the bioethics committees, using the e-mail address of the bioethics committee secretariat, unless the BC concerned specified a different dedicated e-mail address or a different communication method.
3. Occurrence of an event that could affect the safety of specific clinical trial participants is the universal rationale for withdrawing from conducting a clinical trial, in accordance with the applicable protocol, based on Article 37y PF.

1.1.3 Legal analysis of the possibilities arising from a pandemic situation

force majeure et al. - to what extent does the law allow non-standard activities (e.g. electronic submission to the URPL, failure to submit original documents, etc.)?

In the Communication of 24 March 2020, the President of the URPL merely highlighted the rules for electronic delivery of documents that applied before the pandemic, arising under the existing legislation. In the President of the URPL did not propose any new solutions that could address the current situation, and did not allow any exceptions from the obligation to submit original documents. One of the risks associated with the lack of alternative solutions is the extensive (often international) structure of companies in the medical industry, and therefore the problem with establishing an ePUAP trusted profile, permitting to sign documents on behalf of a given entity. The only currently acceptable option would be the use of a qualified electronic signature; however, obtaining it requires appropriate verification, which can be difficult during a pandemic. To sum up, without having one of the two types of electronic signatures, the paths proposed by the President of the URPL are impossible to follow.

1. Representatives of GCPpl, INFARMA and POLCRO shall jointly attempt to enter into dialogue with the President of the URPL, acting on behalf of the associated entities, in order to respond to the needs of the industry and to draw up a temporary derogation from the existing rules during the pandemic.

1.1.4. How to understand the words “promptly” or “without undue delay”

appearing in various official statements and guidelines in the context of the COVID-19 pandemic?

1. The general principle is that “promptly” or “without undue delay” does not mean that the matter is to be dealt with immediately, but as soon as possible, i.e. at the earliest possible opportunity. A body dedicated to handle a case should immediately attend to the case; however, consideration of the case may extend over a period.
2. The terms “promptly” or “without undue delay”, used in the communications and guidelines of the President of the URPL can be traced to Article 35 of the Code of Administrative Procedure (KPA). A public administration body should conduct the

proceedings in an efficient manner, without unreasonably suspending and prolonging its activities, so that the proceedings are closed as soon as possible. This is a kind of instruction for the authorities to consider deadlines set out in the Code of Administrative Procedure [KPA] as maximum deadlines. To sum up: “without undue delay /promptly” according to the Code of Administrative Procedure = as soon as possible, but no later than within the statutory period.

3. On the other hand, “promptly” within the meaning of the Civil Code means that the given action is to be carried out as soon as possible (within a reasonable deadline). A reasonable deadline depends on the circumstances of the case.
4. Pursuant to the current provisions (introduced by the Anti-Crisis Shield 21), cessation and suspension of the time limits in proceedings does not apply to administrative proceedings conducted on the basis of PF regulations, **if failure to issue a decision could cause a threat to human life or health or serious harm to the public interest**. Therefore, due to the entry into force Anti-Crisis Shield 2, the KPA conditions of running time limits in administrative proceedings conducted before the President of URPL and the bioethics commission were restored - **provided for the above-mentioned condition**, including the rest of the deadline for issuing the authorization to conduct a clinical trial and the deadline for issuing consent to make significant changes affecting the safety of study participants in the study protocol or IMP documentation. However, the Anti-Crisis Shield 2, upheld the principle that the deadline for silent settlement does not begin and the commenced remains suspended for the period of the epidemic announced due to COVID-19. In practice, the above means that the sponsor / representative of the sponsor may, in the light of the Anti-Crisis Shield 2, demand from the President of URPL or the bioethics commission to issue a decision within the time limit specified in the PF, although the implied consent does not apply.

1.1.5 What are the legal grounds for changing a clinical study subject visit from a face-to-face one to an e-visit / telephone consultation?

What are the reporting requirements related to this change?

1. According to Article 37y of the Pharmaceutical Act, both a sponsor and an investigator shall abstain from conducting a clinical trial, in accordance with the existing clinical trial protocol, if any event which is likely to affect the safety of the clinical trial subjects occurs, and continuation of participation in the clinical trial according to the existing protocol would endanger the study subjects.
2. The sponsor / sponsor representative should consider whether the change introduced meets the criteria for a substantial amendment. If yes, and there is no time to handle the amendment according to the standard procedure because of the COVID-19 pandemic, the sponsor / sponsor representative shall handle the amendment as an Urgent Safety Measure. Introduction of urgent safety measures should be preceded by a detailed risk assessment with respect to the clinical trial participants and is subject to

¹ Act of 16 April 2020 on special support instruments in connection with the spread of the SARS CoV - 2 virus, which amended the Act of 31 March 2020 on the amendment to the Act on special solutions related to the prevention, counteraction and combating of COVID - 19 , other contagious diseases and crisis situations caused by them, as well as some other acts

obligatory and prompt notification to the URPL and the BC. Hence, Article 37y of the PF should not be universally applicable to multiple clinical trials and study subjects covered by a single decision, and the safety of the participants of each clinical trial should be considered separately.

3. In the absence of an event which is likely to affect the safety of the clinical trial subjects, requiring urgent safety measures to be adopted, the standard procedure as defined by the law in force should be followed. Above all, Article 37x of the PA should be followed, under which making amendments to the clinical trial protocol or to the IMP documentation (which forms the basis for obtaining the trial authorisation), if such amendments are substantial and are likely to have an impact on the safety of the clinical trial subjects, shall require obtaining the positive opinion of the bioethics committee and the consent of the President of the URPL. To recap, there is time to introduce a substantial amendment or an amendment which is likely to have an impact on the safety of the clinical trial subjects, in contrast to a situation where a USM needs to be implemented because the safety of clinical trial subjects is at risk. The introduction of a USM does not require the prior positive opinion of the BC and the consent of the President of the URPL, only notification to the BC and URPL.
4. If the change does not meet the criteria for a substantial amendment, and hence is considered a non-substantial amendment according to point 132 of the Communication from the European Commission – Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1), the amendment does not have to be reported to the BC and URPL. The safety measures adopted during the COVID-19 pandemic that affect the conduct of a clinical trial in accordance with the existing protocol are amendments which may consist in, be caused by or result in one or several deviations from the clinical trial protocol. In order to appropriately assess such changes (especially amendments which meet the criteria for an urgent safety measure – USM – and are therefore subject to the relevant BC / URPL reporting obligations), close cooperation and communication between all stakeholders involved in the conduct of the clinical trial is required, especially between the investigator and the sponsor / sponsor representative, as well as within the structure of the – often global – project team. The scale of amendments may appear insignificant at the local level but may prove significant globally (and consequently the amendments concerned may be qualified as USM and may be subject to the relevant BC / URPL reporting obligations), where similar solutions have been introduced in the context of the COVID-19 pandemic in many states partaking in the conduct of the clinical trial.

1.2 COOPERATION WITH THE BIOETHIC COMMITTEES

1.2.1 Remote meetings of bioethics committees and voting arrangements during such meetings what is the position of the bioethics committees and what are the options under the existing law?

1. In the published Statement of the *Stowarzyszenie Członków i Pracowników Komisji Bioetycznych w Polsce* [Association of Members and Employees of Bioethics Committees

in Poland] on the mode of operation of bioethics committees during the state of epidemic in Poland, the Association appeals for and submits procedural suggestions as regards the transition to remote operation of the bioethics committees.

2. Under the current regulations in force in Poland (Regulation of the Minister of Health and Social Welfare of 11 May 1999 on detailed principles for appointing and financing as well as the mode of operation of bioethics committees, and the Code of Administrative Procedure KPA), conducting meetings remotely by the bioethics committees is significantly hindered. However, as shown by the experience of bioethics committees that have not ceased their activities, such meetings are possible under certain conditions:
 - 1) Communication can be carried out via exchange of emails, using the commonly accessible electronic communication tools, teleconference, video-conference and other ICT solutions, as long as they safeguard confidentiality / ensure that access to the information is provided only to specific participants / recipients.
 - 2) The regulation includes a provision (Article 6(5)) stating that the bioethics committee shall adopt a resolution expressing its opinion by secret ballot. Therefore, it is recommended to consider the following scenarios:
 - the preferred option, if it is feasible and safe for BC members: after the BC meeting agenda has been covered (via the Internet), the chairperson announces the initiation of a secret ballot on the projects and specifies the duration of the ballot, e.g. 24 hours. During this period each BC member should individually arrive at the ballot box at the BC premises, cast their vote and leave signed attendance lists (previously sent via e-mail). After the ballot deadline has passed, or earlier, once all BC members have cast their vote, an employee of the bioethics committee opens the ballot box, counts the votes and forwards the results by e-mail to the chairperson of the meeting, who promptly sends the ballot results to all BC members by e-mail and closes the meeting;
 - alternatively – use of electronic tools, e.g. the Gmail mailbox (free) features forms that, when completed, could allow for secret voting (questions can be added to the form to create a survey);
 - alternatively – the person responsible for the ballot (BC employee) can collect the votes of members of the BC via e-mail; such a ballot, however, does not meet the secrecy requirements in accordance with the legislation in force.
 - 3) According to Article 6(7) of the abovementioned regulation: “Resolution of the bioethics committee shall be signed by members who participated in the adoption thereof.” On the other hand, Article 7 of the abovementioned regulation stipulates that “the Chairperson of the bioethics committee shall immediately forward a resolution expressing the opinion to the entity intending to conduct a medical experiment.”
3. In addition, in the context of the case-law of administrative courts, it has become common practice that the activities of bioethics committees are governed by the provisions of the KPA and that resolutions of the bioethics committees are considered

to be administrative decisions, therefore the necessary components of such decisions should be considered in the light of the provisions of the KPA. Article 107 of the KPA defines the following components of such decisions: “signature, name and surname, and job title of the employee of the body authorized to issue the decision, and if the decision was issued in the form of an electronic document - a qualified electronic signature”. If a member of a bioethics committee working remotely does not have a qualified signature, he or she may sign a “separate” attendance list, provide a scan of that list, and deliver the original list to the bioethics committee as soon as possible (e.g. after the pandemic).

4. Pursuant to the current provisions (introduced by the Anti-Crisis Shield 2 provisions), suspension and cessation of the time limits in proceedings does not apply to administrative proceedings conducted on the basis of PF regulations, **if failure to issue a decision could cause a threat to human life or health or serious harm to the public interest**. Therefore, due to the entry into force of Anti-Crisis Shield 2, the KPA conditions of running time limits in administrative proceedings conducted before the President of URPL and the bioethics commission were restored - **provided for the above-mentioned condition**, including the rest of the deadline for issuing the authorization to conduct a clinical trial and the deadline for issuing consent to make significant changes affecting the safety of study participants in the study protocol or IMP documentation. However, the Anti-Crisis Shield 2, upheld the principle that the deadline for silent settlement does not begin and the commenced remains suspended for the period of the epidemic announced due to COVID-19. In practice, the above means that the sponsor / representative of the sponsor may, in the light of the Anti-Crisis Shield 2, demand from the President of URPL or the bioethics commission to issue a decision within the time limit specified in the PF, although the implied consent does not apply.

1.2.2 Are electronic submissions of applications/documents to the bioethics committees possible, and if so, by which means?

1. Based on KPA (Article 14(1)), the written form of service to and from bioethics committees must be maintained in the vast majority of cases (an electronic document bearing a qualified signature is an exception). However, to enable / facilitate the operations of bioethics committees and the ethical evaluation system during the COVID-19 pandemic, the following procedure is recommended:
 - 1) Notifications (not requiring any opinion to be issued by the bioethics committee) can be sent to the e-mail addresses indicated. After the pandemic, when the previous method of service can be restored, the documents should be submitted collectively in the required written form, as per the KPA.
 - 2) In the case of applications requiring the opinion of the bioethics committee, it is necessary to maintain the current method of service in writing. However, in order to facilitate / speed up the procedure for processing applications, parallel correspondence to the indicated e-mail addresses is recommended.
2. For large files (e.g. IB, DSUR), it is recommended to send them in .zip format.

1.2.3 Is it possible to confirm receipt of documentation by the BC by e-mail?

Some bioethics committees had already done this before the COVID-19 pandemic - a cover letter was printed, signed, scanned and sent back to the applicant's e-mail address. Some bioethics committees prefer simple emails that specify which documents have been submitted.

1.2.4 Reporting Suspected Unexpected Serious Adverse Reactions (SUSAR) during the COVID-19 pandemic

1. The general principles for submitting notification types are recommended here:
 - Notifications (not requiring any opinion to be issued by the bioethics committee) can be sent to the e-mail addresses indicated. After the pandemic, when the previous method of service can be restored, the documents should be submitted collectively in the required written form, as per the KPA.
2. In addition, to facilitate the work of bioethics committees, it is recommended to arrange the submitted documents according to study protocols (a separate e-mail for each protocol).
3. Sometimes information concerning the safety of use of medicinal products (including SUSARs) is reported with bioethics committees via dedicated platforms. This solution can be used as an alternative to e-mail communication, if there is an agreement over this matter between the Sponsor / CRO and the bioethics committee concerned.

1.2.5 What to do if the bioethics committee regulations do not allow remote meetings?

1. The aforementioned Statement (of the Association of Members and Employees of Bioethics Committees in Poland) suggests a scenario for prompt amendment of BC regulations – either for committees established by universities and institutes or regional medical chambers.
2. If it is not possible to change the committee's regulations quickly, the following solutions should be considered:
 - 1) Creating an attachment to the regulations specifying the conditions for conducting remote meetings
 - 2) Obtaining consent for a temporary deviation from the regulations, in accordance with the procedures of the bioethics committee concerned (before each meeting or once for the entire duration of the COVID-19 pandemic).

1.2.6 What are the possible solutions that a bioethics committee could adopt immediately after the COVID-19 pandemic, when we are likely to encounter an accumulation of applications submitted for evaluation?

1. Bioethics committees could possibly double the number of meetings for a period equal to the duration of pandemic-related restrictions. For example, if the restrictions continue for 4 months, bioethics committees would intensify work for the 4 months following the pandemic. If a bioethics committee meets once a month, it would have two meetings a month for 4 months after the end of the pandemic.

2. Bioethics committees could continue working during the summer months (July - August), especially if the pandemic-related restrictions are lifted by then.
3. If a bioethics committee decides not to organize any meetings in the summer months, the period of increased activity (meetings taking place twice as frequently – refer to clause 1) should start from September (provided that the pandemic-related restrictions are lifted by then).
4. In the event of accommodation, logistical or other shortages that would prevent doubling the frequency of BC meetings in the standard format, the option of remote meetings could be used, as tried and tested during the COVID-19 pandemic.

1.3 COOPERATION WITH THE URPL

1.3.1 How to proceed when access to experts is limited (URPL reviewers)? (Availability of URPL reviewers, workload on reviewers)

1. As at 23/03/2020, the URPL confirms that there are no delays in the review process.
2. Sending documentation to reviewers electronically / in electronic form
3. As recommended by EMA - sponsors should consider the workload of reviewers and send only correct and complete applications / documentation, comprising only necessary amendments. Over-reporting should be avoided. This requirement not only applies during the COVID-19 pandemic but should also be followed for several months after the pandemic-related restrictions have been lifted, during which we may witness an accumulation of outstanding applications/documents submitted to the URPL.

1.3.2 Requirement to submit original documents (powers of attorney and CV) to the URPL

- are there any alternative solutions during the remote work of sponsors, CRO companies and the URPL?

1. Use of an electronic signature in the EU under eIDAS (Electronic Identification and Trust Services Regulation) or the use of an equivalent electronic signature outside the EU, which meets all the requirements of an electronic signature.
2. Referring, if possible, to the original corporate identity documents previously submitted to the URPL.
3. Downloading corporate identity documents of the sponsor / legal representative of the sponsor, whether free-of-charge or otherwise, from the commercial register (Delaware statement does not meet the criteria of a corporate identity document; in the case of documents downloaded for a fee, make sure that they are signed and not only a printout from the register). In addition, in some countries, documents are generated with a code that allows later verification of the document during review of the application.
4. Investigators can use the “signer” option (trusted signature), which allows you to send correctly signed documents (e.g. CV) by email to the Sponsor / CRO to submit a complete dossier

<https://www.gov.pl/web/cyfryzacja/podpisz-dowolny-dokument-wykorzystaj-do-tego-profil-zaufany>

1.3.3 Are electronic submissions to the URPL possible, and if so, by which means?

The Communication message of the President of the URPL on electronic submissions of documentation:

<http://bip.urpl.gov.pl/pl/urz%C4%85d/za%C5%82atwianie-spraw/elektroniczny-urz%C4%85d-podawczy>

and

<http://urpl.gov.pl/pl/komunikat-prezesa-z-dnia-24-marca-2020-rw-sprawie-trybunsk%C5%82adania-dokumentacji-do-urz%C4%99du>

2. ePUAP:
 - ability to attach large files
 - make sure to use a general letter to the URPL
3. Mail up to 5MB
4. Files recorded on a disc (submission to the URPL in person)

1.3.4 Prioritizing submissions (new studies, substantial amendments) - common criteria

1. It is recommended to limit the submission of new studies and amendments to ongoing studies that are not urgent.
2. Trials submitted under the Voluntary Harmonisation Procedure (VHP), if they can wait, can be submitted after the deadline stipulated in the *Guidance document for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications*. According to URPL recommendations, failure to meet the deadlines set out in the guidelines for VHP cannot be a basis for the URPL to reject the application; our national law does not provide for such a situation.
3. Priority is given to:
 - applications related to COVID-19, both submissions of new studies and any amendments introduced to ongoing studies as a result of the pandemic
 - substantial amendments related to patient safety in ongoing studies
 - safety reports (SUSAR, DSUR)
 - extension and other studies, which should start without delay due to the high benefit / risk ratio
4. For several months after the COVID-19 pandemic, once the pandemic-related restrictions are lifted, we may expect an accumulation of outstanding applications / documents submitted to the URPL. We recommend refraining from over-reporting during this period, especially in the context of submissions of non-substantial amendments to the URPL. According to point 132 of the Communication from the European Commission – Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1), "the sponsor does not have to notify non-substantial amendments to the national competent authority or the bioethics committee. However, non-substantial amendments should be recorded and contained in the documentation when it is subsequently submitted, for example in the subsequent notification of a substantial amendment."

1.3.5 Silent approval - if and how does it work during the COVID-19 pandemic?

* Implicit consent => initial applications

* Implicit consent => substantial amendments

According to the applicable law (unchanged despite the entry into force of the so-called Anti-Crisis Shield 2) during the period of the epidemic, the deadline for silent settlement of the case does not start, and the commenced is suspended for this period. The authority may issue a decision in cases conducted on the basis of PF, including in particular the permission to conduct a clinical trial and consent to make significant and affecting the safety of study participants changes in the study protocol or documentation regarding the IMP. In practice, the entry into force of Anti-Crisis Shield 2 means that the sponsor / representative of the sponsor may request the President of URPL or the bioethics committee to issue a decision within the time limit specified in the PF, although the implied consent does not apply.

In consideration of the above, the URPL is expected to facilitate effective e-mail / telephone communication after the pandemic, in order to allow confirmation of the trial assessment status. In turn, applicants are expected to submit correct and complete documentation and, where possible, accumulate several amendments in one submission and refrain from over-reporting. E-mail communication with the URPL to monitor the progress of the case.

1.3.6. Request to the President of the URPL for electronic submission

when it is difficult to receive documents sent by fax and delays in paper delivery are anticipated

In the case of pending proceedings, it is possible to apply to the President of the URPL, pursuant to Article 39 with superscript 1. § 1. point 2 of the KPA, for submission via electronic means of communication (in relation to proceedings where no electronic submissions were sent via an electronic inbox). Please remember to provide the electronic address for delivery in the request.

1.3.7 What approach should be used when submitting Urgent Safety Measures in accordance with Article 37y of the PF?

If and when to submit a (substantial) amendment to the study protocol?

1. According to the EMA guidance on the management of clinical trials during the COVID-19 pandemic ("List of recommendations and guidelines" section in the introduction):
 - amendments requiring immediate action are introduced as an urgent safety measure (USM).
 - changes which are not urgent and can be implemented over a longer period of time should be submitted in the form of substantial amendment (if they are subject to reporting according to the law in force).
2. This approach is also consistent with the Communication of the President of the URPL of 19 March 2020 ("List of recommendations and guidelines" section in the introduction).

1.3.8 Suspending and resuming patient recruitment due to the COVID-19 pandemic - does it require a substantial amendment? How to report them?

Suspension of recruitment is due to reasons attributed to the work organization at the study site and the need to implement general safety measures in response to the pandemic, and not for safety concerns related to Investigational Medicinal Products (IMPs). Since recruitment is not suspended due to safety concerns related to the use of IMPs, its resumption does not qualify as a substantial amendment and does not require the consent of the URPL.

2. CLINICAL ACTIVITIES AND MANAGEMENT OF ONGOING STUDIES

2.1 STUDY SITE

2.1.1 Patient visits

2.1.1.1 Risks related to conducting the study during the COVID-19 pandemic

1. Safety and risk-benefit ratio analysis (in consideration of the increased risk versus therapeutic and other benefits) should be conducted for each study and study site during the COVID-19 pandemic:
 - a) The sponsor should assess the risk-benefit ratio of the IMP used in the study during the pandemic, and the study design (e.g. frequency of visits, the need to perform all study procedures) in terms of patient safety and limited access to study sites or diagnostic facilities, and send appropriate instructions to the investigators
 - b) The site / principal investigator should assess the risk based on:
 - epidemiological status in the area where the study site is located, and the patients reside;
 - health status of individual patients especially concomitant diseases and drugs, patient's age and patient's social status
 - other factors that increase the risk of infection and affect overall patient safety
 - the ability to perform the most important study procedures (regarding patient safety and critical data collected in the study)
2. All conclusions and recommendations should be promptly communicated between the sponsor and the study site / investigator. They can be modified at any time.
3. Deviations from the protocol (if necessary) should be communicated as soon as possible by the site's study team to the monitor (CRA) assigned to the trial/ sponsor.
4. The study site should keep records of all changes and decisions sent by the sponsor and initiated by the study site.

2.1.1.2 Patient in quarantine with suspicion of COVID-19

1. A patient in quarantine should not have a visit to the study site or any home visit (unless absolutely necessary for their health or life). The investigator should report such a case to the CRA / sponsor with information about whether the test was performed, and the COVID-19 infection was confirmed.
2. After the quarantine, the patient should be contacted immediately by telephone to make sure that there are no symptoms of the infection and the patient can visit the site. If possible, a SARS-CoV-2 test should be performed to rule out that the study participant carries the virus.
3. Even after the quarantine, consideration should be given to the option of a telephone visit or, if this is not possible, to minimize contact with other patients and study staff. During the visit, the study site should provide protective equipment for the study team as well as the study participant, especially if the patient did not have the SARS-CoV-2 test done.

2.1.1.3 Patient with confirmed SARS-CoV-2 infection

1. The study site / investigator should immediately report every COVID-19 infection to the monitor / sponsor as AE or SAE (assessing the degree of risk to the patient's health and life)
2. Together with the medical monitor ("study physician"), consider the risks and benefits of continuing patient participation in the study, and determine what to do next if the patient is to continue participating or is to withdraw from the study (e.g. introducing telephone visits to collect information on patient safety – so called safety follow-up).
3. The study site should assess the risk of further spread of the virus before obtaining information about the patient's infection and take appropriate measures in accordance with sanitary and epidemiological requirements. This infection risk assessment and the relevant measures taken should also be reported to the monitor / sponsor.
4. If a site needs to be closed or the quarantine of a site staff is needed, quick action is needed to secure medical care and monitor the safety of all patients - participants of clinical trials currently being conducted by the site. Chapter 2.1.3 details the proposed solutions.

2.1.2 Limited availability / absence of members of the study team

1. The investigator should quickly verify what part of the study team is available and whether it is possible to continue the study. If yes, and after making sure that it is safe to be at the study site, the patient visits can take place.
2. If it is not possible to carry out some of the study procedures during a visit, consideration should be given to
 - performing only those study procedures that can be performed
 - in the case of study staff (e.g. Investigator) in quarantine - performing a remote patient visit from the place of isolation, documenting the remote visit or dictating description of the visit to a person present with the patient at the site (appropriate documentation of this process)
 - finding a qualified person who, after training by the investigator / and / or CRA, will join the study team
 - delaying the visit (especially if the person's quarantine will be completed within a certain time that allows to perform patient's scheduled visit)
4. The study site / investigator, regardless of the availability of individual members of the study team, should secure contact with the patient, for example to collect information about the patient's health and safety
5. When adding a new member of the study team, the Sponsor's requirements and standards should be followed, including
 - training in study procedures
 - completing the document certifying that the investigator has assigned specific tasks to the study team members (Delegation Log)
 - obtaining the required access to systems, platforms and other tools as a matter of urgency, e.g. IVRS, eCRF (necessary support of CRA).

6. Job rotation of the site staff (remote alternate with onsite work) is recommended to reduce the risk of SARS-CoV-2 infection of the study staff
7. In exceptional cases, consideration should be given to the transfer of patients to another clinical study site in consultation with the Sponsor and after obtaining the consent of the study participant.
8. All such changes and extraordinary measures should be properly documented in the medical records of the clinical trial participant.

2.1.3 Administrative closure of outpatient study sites

1. Determining the reason and period for closing the study site
2. Informing the bioethics committee and the sponsor
3. With short-term closure, postponing visits until the study site is reopened while maintaining remote contact with the patients
4. With long-term closure of the study site, consider the benefit-risk ratio as to whether the patient should continue participation in the study
5. It is recommended that study site proactively proposes solutions to the sponsor, i.e.
 - discontinuation of patient follow-up,
 - transfer of patients to other clinical study sites (ensuring patient transport and access to patient records),
 - transfer of the principal investigator and study team to another site, starting a new study site for the time being (remote visits during the transitional period, accelerated procedure of study site selection, submitting an application of changes in the conduct of the trial, training and initiation)
 - home visits of the study team (to be decided and approved by the QA sponsor or CRO)
 - transfer of ad hoc patient care, with the possible extension of the study team to include local doctors, e.g. Primary Health Care (POZ) or Outpatient Specialist Care (AOS) supported by coordinators from the primary study site and in the long run the launch of a satellite study site under the supervision of the current principal investigator or a designated deputy

2.1.4 Remote visit / by phone advice / e-advice of a clinical trial participant

1. The basis for providing by phone advice along with stationary medical advice in outpatient units may be the provision of the Regulation of The Minister of Health of 31 October 2019, which considers medical advice provided in direct contact with the recipient or remotely using ICT systems or communication systems.
2. In addition, the Act of March 2, 2020 (especially the amendment from March 31, 2020) on specific solutions related to the prevention, prevention and eradication of COVID-19, other infectious diseases and emergencies caused by them, in paragraph 7 describes in detail the rules for the provision of healthcare services under by phone advice (using the Central TC advise System provided by CSIOZ).
3. To prepare by phone advice or teleconsultation, you can use the message and practical recommendations of the Council of General Practitioners (Kolegium Lekarzy Rodzinnych).

2.1.5 Visits of sponsor's representatives (including monitors) in the study site

Limited availability of site staff

1. It is important to ensure the continuity of the study, supervision of procedures and communication with the sponsor / CRA.
2. It is recommended to use the RBM (Risk Based Monitoring) strategy; the sponsor should indicate key areas to be covered during the monitoring remote visit. Monitoring visits by phone and video conference can be conducted with the use of available applications and tools but without unnecessarily increasing the study team workload.
3. The study site should indicate the main contact person for the monitor "Site Crisis Contact Person – SCCP".
4. The dates and frequency of telephone contacts should be established (e.g. once every 2 weeks - 15 minutes) along with the topics limited to the most important issues related to supervision of the ongoing clinical trial, i.e.
 - patient access to the study team
 - new SAE cases and supervision of patient safety
 - deviations from the protocol
 - IMP (quality and quantity) status
5. It is recommended (if possible) to keep electronic (e-mail) mail to a minimum, limited to safety information, and to suspend paper-based mail (DIL / SUSAR listing instead of the entire CIOMS reports).
6. It can be proposed to create a communication platform using modern technologies (e.g. MsTeams, SharePoint) containing up-to-date information and recommendations from the sponsor regarding the study (make sure that each team member has access to it at any time).
7. It is a good solution for SCCP to additionally keep a site "diary", documenting the current status of the study site (status of the study team, problems, measures taken).
8. The same "diary" should be kept by the sponsor / study monitor

2.2 PATIENT RECRUITMENT

2.2.1 Suspension of screening and randomization

According to the statement (Guidance on Management of Clinical trials during the COVID-19 pandemic from EMA, GCP Inspectors, CTFG, CTEG dated 20Mar2020), the possibility of starting a new clinical trial or including new trial participants in an ongoing trial should be critically assessed by sponsors. All decisions to adapt the course of a clinical trial should be based on a risk assessment by the sponsor (according to ICH GCP section 5.0). The sponsor is expected to carry out a risk assessment for each ongoing study and the investigator is expected to analyse each participant and implement appropriate measures that prioritize participant safety and data validity. In the case of a conflict, the subject's safety always prevails.

2.2.2 Resuming screening and randomization

1. During the period of lifting restrictions associated with the COVID-19 pandemic, sponsors should be aware of current pressures on the medical profession and medical staff and should carefully assess the possibility and relevance of including new study

participants in ongoing clinical trials. Absolute priority should be given to clinical trials for the prevention or treatment of COVID-19 and COVID-19 related diseases, or studies for serious diseases without a satisfactory treatment option.

2. In the event of screening re-opening, the investigator should assess the capacity of the site and research team to continue including patients. If it is necessary to add new team members, they should receive appropriate training and access to any systems and platforms used in the study.
3. It is important to ensure the availability of laboratory kits, test product and additional drugs, as well as any equipment for the patient (e.g. Diaries, e-PRO devices) that are necessary for conducting the clinical trial (e.g. to enable registration, monitoring the safety of participants and treatment efficacy, providing data on study endpoints). Therefore, it is recommended to maintain an adequate supply of these devices in case of distribution failure. In addition, changes in the distribution of these devices between sites may be necessary.
4. It is recommended to regularly review recruitment plans at site and country level so that the sponsor can analyze the planned recruitment in the study and take appropriate decisions and actions to complete the project.

2.3 STARTING A NEW STUDY AT A STUDY SITE

2.3.1 Study sites activation is impeded due to the inability to conduct the initiation visit on site.

1. Initiation visits at study sites can be now postponed according to forecasts for the region and / or for individual countries, as per sponsor's instruction
2. However, if in the sponsor's and investigator's opinion remote activation of the site is pivotal (e.g. when the benefit to patients from participation in a new study outweighs the risk associated with visits to the site), the Sponsor and / or CRO in agreement with the Investigator shall determine:
 - additional resources not included in previous arrangements, necessary to enable conducting a clinical trial at a given site after activation
 - the need to modify previous declarations related to the predicted recruitment goals and the time of their achievement
 - the form of conducting an initiation visit at site (i.e. visit at the site, remote visit, using dedicated IT tools or a hybrid solution - identification and implementation of necessary activation activities at the site in combination with remote actions).
3. If additional resources necessary to conduct a clinical trial at given site are identified, the Investigator in agreement with the Sponsor / CRO and after analysing the protocol may consider modifying the composition of the Site Staff and the locations of performing study procedures so that part of the tasks related to conducting the clinical trial is outsourced as a service to subcontractors or at a satellite sites (including entering data into eCRF, nursing home visits, diagnostic tests, specific medical procedures, drug delivery to the study Subject's place of residence).

2.3.2. Monitoring visit at the site after the first Participant has been included.

1. The Sponsor and / or CRO in agreement with the Investigator shall determine the form of conducting the monitoring visit after the inclusion of the first Subject. When choosing

the form of the visit (at the site, remotely or in combination of both), the following should be considered:

- i. critical elements of the study documentation requiring verification based on Risk Based Monitoring and / or other analytical tools indicating the necessary areas for monitoring
 - ii. technical and infrastructural possibilities of the site to perform the given form of visit
 - iii. meeting formal requirements to conduct a specific form of visit
 - iv. the scope of time in which the given form of visit involves the Site's staff
2. Additional guidelines for monitoring clinical trials and critical data for the safety of Study Subjects are described in sections 2.6 and 4.1, respectively.

2.4 PATIENT INFORMED CONSENT FOR CLINICAL STUDY

2.4.1 Inability to quickly obtain a participant's re-consent to new procedures

1. Risk versus benefit analysis should be performed and consideration should be given to promptly informing the patient of planned changes and procedures that eliminate/ decrease risks.
2. There may be a need to obtain another consent from study participants already enrolled (re-consenting). However, patients should not have to visit the study sites in order to give another consent.
3. If it is necessary to implement new urgent changes in an ongoing clinical trial (e.g. expected mainly due to the COVID-19 pandemic), alternative methods of obtaining such patient consent should be considered during the pandemic, e.g. contacting study participants by telephone or videoconference and obtaining oral consents supplemented by email confirmation. Informed consent is a continuous process between the investigator and the patient / participant. The investigator should keep the participants informed about any findings that may affect the patient's willingness to participate in the study. Most measures taken to ensure the safety of study participants do not require additional patient consent. Under special circumstances related to the pandemic, the study sites may attempt to document the patient's consent in a remote form which, once the extraordinary circumstances have come to an end, will be able to be confirmed once again, for example by making an entry signed by the patient to the patient's medical records.
4. In a situation where a substantial change to the study protocol must be introduced or new safety information is available, the patient must be informed of these amendments and agree (re-consent) to continue participation in the study.
5. The preferred approach is to obtain written consent, but if the patient cannot visit the study site, this may be difficult.
6. In order to obtain consent for continuation of the study in consideration of the change, the investigator can contact the patient directly, by phone, by email, depending on the situation and options available.
7. The proposed solution is to send a new version of the consent in a paper version to the patient, e.g. by courier service. Once the documents are delivered to the patient, the investigator should call the patient, explain the reason why the patient must decide

again on whether to participate in the study and discuss all changes / information contained in the new version of the consent. The patient should be able to ask questions and get answers to address any doubts.

8. If the patient agrees to continue participation in the study, the patient signs two consent forms received and sends them by courier / post to the investigator / study site.
9. The investigator signs the informed consent form at the date of receipt and describes the process of obtaining patient's consent in the medical records.
10. In critical situations, in many cases the sponsor/CRO may consider that the introduced change takes place pursuant to art. 37y PF/ art. 51 of the Act on Medical Devices - then it does not require URPL's permission or the opinion of the bioethics committee instead, the bioethics committee and the URPL should only be notified. It might be (but don't need to be) situations where the patient must be quickly informed about changes in the conducting of the study (e.g. delivery of drugs from the study site directly to the patient, rescheduled visits, change of laboratory or the amount of blood drawn for testing). The proposed solution is each time to:
 - Either recognition that we operate pursuant to art. 37y PF / art. 51 of the Medical Devices Act - then informing about the new process of the bioethics commission and the URPL as well as informing the patient by phone and obtaining his consent, provided that the given change concerns him. The investigator / interviewer is required to record the details of the interview in the medical records and obtain post factum consent in the form of prior written confirmation of oral consent
 - Either recognition that the change is included in the definition of insignificant changes (if it falls - see CT-1 guidelines, sections 3.2 to 3.6) - then they should be implemented, without the need to inform URPL and the bioethics committee

2.5. PERFORMANCE OF LABORATORY TESTS

In each clinical study you may need to perform critical laboratory tests, imaging or other diagnostic test critical for patient's safety. If the study participant cannot arrive at the study site to have the tests performed, it is acceptable to perform the tests at an authorized / certified local laboratory (or at an appropriate clinical site where other studies are conducted) (in accordance with the national law). The investigator / study site should inform the sponsor of this possibility and of such cases without delay. Laboratory tests can be performed in local laboratories and their results can be used to make safety-related decisions. If this is the endpoint of the study and the samples cannot be sent to a central laboratory, the analysis should be performed locally and then explained, evaluated and reported in the clinical study report (according to ICH E3) and EMA guidelines for data management during the epidemic, see 'List of recommendations and guidelines'

Participants of a clinical trial should be immediately informed about any deviations from the study procedures that directly concerns the participant and should give their consent (or object). This process should be described in detail in the patient's/clinical study participant's medical records.

2.5.1 Lack of possibilities to ship to the central laboratory (if applicable for a given clinical trial)

Algorithm for handling laboratory samples in critical situations (e.g. COVID-19 pandemic)

1. Tests significant for monitoring of therapy safety (laboratory safety tests)
 - 1) If you cannot send samples to a central laboratory, consider sending them to local laboratory:
 - hospital laboratory if the study site is in a hospital
 - another laboratory that meets the criteria of quality standards in accordance with the Regulation of the Minister of Health of 23 March 2006, as amended. The use of laboratories with ISO 17025, ISO 15189 quality certificates and experience in clinical trials in accordance with Good Clinical Laboratory Practice (GCLP) should be preferred
 - 2) If samples cannot be collected at the study site:
 - The patient should be directed to a blood collection unit of a local laboratory (e.g. network laboratory, for the reason given above)
 - Biological samples should be collected at the patient's home by:
 - ✓ Study site nurse
 - ✓ A nurse from a nearby blood collection unit
 - 3) If it is possible to use a laboratory kit from the central laboratory, follow the instructions sent by the central laboratory.
 - 4) If, for technical reasons, the materials in the central laboratory kit provided as part of the clinical trial cannot be used, blood should be collected according to the testing laboratory procedure.
 - 5) Interpretation of the test results should be made according to the test laboratory reference values.
2. Specialized medical tests other than the need of safety monitoring (e.g. pharmacokinetic analyses)
 - 1) The procedure should be agreed with the central laboratory
 - 2) Specify storage conditions for biological material
 - 3) Agree on the conditions for collecting the samples by a courier service (including the change of samples pick up location)
3. Each change of the procedure should be properly documented in accordance with the SOP of the study site regarding the collection of biological material (checklist, form) if a site has one.
4. Sending samples to the central laboratory should be contracted accordingly. Sponsor should conclude an appropriate contract with the supplier of the laboratory and / or transport service the study site should obtain the sponsor's consent to cover the costs, if the service is organized by the study site.

2.5.2 No dry ice supply

1. Extending the period of storage of samples at the study site / postponing the shipment
2. Confirmation of the procedure with the sponsor
3. Consider another local dry ice supplier

2.5.3 Samples not collected due to limited availability of medical staff

1. Quick sponsor response to determine the possibility of postponed/delayed collection of samples

2. Finding a qualified person who, after training by the investigator and/or CRA, will join the study team and follow the algorithm (Chapter 2.1.2)

2.5.4 Unable to collect samples from study sites / couriers not admitted to study sites

1. Ensuring longer storage of samples
2. Providing an alternative option for collecting shipments by study sites - pickup points (security, concierge, etc.)
3. Performing analyses at a local laboratory

2.5.5 Not enough kits in the study site to collect biological samples

1. Prioritize securing of analyses involving safety tests and clinical trial endpoints (if assessed using laboratory test results)
2. Transfer kits from another study site
3. Use test tubes/containers from other kits allocated to subsequent patient visits or use standard test tubes available at your site.
4. Alternatively, use of standard tubes used by the site

2.6 CLINICAL STUDY MONITORING

2.6.1 The sponsor's obligation to oversee and monitor the conduct of the study

1. Some sponsor responsibilities, such as supervising and monitoring the conduct of a clinical study, and quality assurance activities are still necessary, but need to be reassessed and may require modification and introduction of temporary alternative methods and processes.

2.6.2 Clinical Monitoring Plan Amendment

1. It is vital to adapt the site monitoring plan, supplementing it with (additional / increased) remote / centralized monitoring and remote / central data review, if possible and appropriate in the given situation. Monitoring visits can be conducted by phone and videoconferencing with the use of tools such as Centralized Monitoring, Site Management Calls, Remote Monitoring; the sponsor needs to indicate key areas to be covered during a remote visit (without unnecessarily increasing the workload on the site staff). It is necessary to review and update, if applicable, the contract with the investigator / study site (and Plan Monitoring) and check if there are no conflicts that need to be addressed;
2. The sponsor should consider the scope and type of monitoring that would be possible in any particular study in this exceptional situation and compare it with the additional burden that any alternative measures would impose on staff and sites. The monitoring plan should then be amended in accordance with these considerations, to achieve an acceptable balance between adequate oversight and the capabilities of research sites.
3. It is necessary to train the clinical study team (CRAs, Project Managers) and communicate with the study sites in order to determine new methods of monitoring and supervision of clinical trials at the study sites.
4. Consider the backlogs with source data verification (SDV) as a project risk and the use of temporary alternative forms of monitoring (e.g. possible temporary or permanent reduction of the SDV level)

5. Consider threats to timely database closure (DB Lock) as a project risk. It is important to efficiently transfer information from study sites and from CRAs about the current situation and the possibility of the study site performing its tasks related to the upcoming DBL (access to medical records for the purpose of SDV, responses to data queries)

2.6.3 Applying Risk Based Monitoring (RBM) Strategy

1. The method recommended for supervising the progress of the trial and monitoring patient safety is risk-based monitoring which includes centralized monitoring and central review of collected data. Centralized monitoring of data collected by electronic data systems (e.g. eCRF, central laboratory or ECG / imaging data, ePRO, etc.), provide additional monitoring capabilities that can compliment and temporarily replace on-site monitoring by remote evaluation of current and / or aggregate collected data from sites in real time. Additional off-site monitoring activities may include telephone calls, video visits, emails, or other online tools to discuss the process with the investigator and site staff. These activities can be used to obtain information on the progress of a clinical trial, exchange information on problem solving, review procedures and study participant status and to train investigator or site staff.
2. As part of remote monitoring visits, it is generally not recommended to conduct SDVs of medical documentation within the meaning of Polish regulations, e.g. by scanning source documents. It is permissible to verify other documentation that is not medical documentation within the meaning of the regulations (and does not disclose the patient's identity) - e.g. lists documenting the current quantity of the investigational medicinal product in the study site, storage conditions, etc.
Although remote access by CRA to site files or source data (SD) as Urgent Safety Measures is not a recommended or often technically impracticable, the sponsor / CRO may consider it as the last resort and under strictly defined rules, in consultation with its QA and legal department to ensure compliance of the proposed technical solutions with the regulations on medical documentation and the protection of personal data of the clinical trial participant.
3. For remote monitoring to have a real chance of success, it is advisable to agree on timely and disciplined data entry by the study team in the electronic CRF system (EDC) and other tools following signed contractual requirements. It is necessary to emphasize the importance of timely entry of data so that it is possible to review them regularly and obtain information on visits and the status of study participants. Regular data entry will also contribute to reduction in the number of telephone contacts with the study site made to obtain certain data orally by the CRA.
4. It is recommended to adapt requests to the site study team regarding less important study issues such as supplementing study records (missing CVs, GCP certificates etc.) to the current situation (workload and availability of the site staff)
5. Where possible, extending CRA access to listings and reports from central systems/ establishing regular reviews, which would produce the widest possible view of the status of patients in the study without having to contact the study site (condition: timely data entry and compliance with other study procedures, e.g. sending laboratory results obtained locally, document scans to central vendors etc.).

6. With reference to the abovementioned point - written summaries of the findings/ deviations are essential, possible telephone contact again if the findings are critical or serious.
7. Reporting contacts with study sites
 - Consider a temporary change of the rules for auto-queries and/ or central deletion of unnecessary queries by DM based on guidelines from the central clinical data management team to relieve study sites
 - Interim Analysis / DBL: re-evaluation of the completion feasibility within agreed deadlines, considering new risks such as the lack of on-site visits. Complete postponement or division into stages according to feasibility in the countries.
8. Creating an emergency plan in case the situation turns out to be uncontrollable/ irreparable, resulting in the inability to conduct the study at a given study site or throughout the country. Preparation of a notification template for the URPL, bioethics committee, investigator and study site management (if applicable) concerning study suspension/discontinuation at the study site / throughout the country. Securing personnel in the organization who will be able to perform such notification.
9. In some cases, the sponsor may encounter restrictions due to the limited availability of study team attributed to the current epidemiological situation in the study site (e.g. quarantine of the study team, reclassification of a ward into a special-purpose hospital, etc.)
10. It will be crucial to maintain constant contact with the staff available at the study site. Remote monitoring process can be limited only to key data and processes (e.g. SAEs, AEs related to SARS-COV-2019, processes required to continue participation in the study and to supervise safety of clinical trial participants)
11. After such contact, it is recommended to provide a written summary of findings/ deviations after data review (CRF, listings, vendor reports); another contact by phone should be made if any critical findings are identified, in keeping with sponsor procedure
 - Maintain "common sense" in the number and length of telephone contacts with study sites (ad-hoc contacts)
 - Reporting contacts with study sites
12. In a critical situation, the investigator may consider extending the study team, e.g. temporary employment of a freelance clinical study coordinator or doctors of other specialties in order to ensure continuity of the study team's work. Clinical trials in which intermediate or final database closures are planned require an analysis of the feasibility and correctness of this process. If such a risk is considered, the deadline may need to be postponed or the process may need to be implemented stage-wise in specific countries. If possible, qualitative changes in the requirements regarding DBLs should be introduced and the focus should be on collecting strategic data, while less attention and restrictions in the approach should be presented in relation to e.g. signing pages.
13. It is important to efficiently transfer information from the study sites and from clinical trial monitors about the current situation, sponsor's guidelines and the ability of the study site to fulfil the tasks associated with the upcoming closure of the database (access to medical records to respond to data queries)

14. Sponsors should also prioritize clinical projects, take actions to reduce "losses" of study data during the period of chaos, e.g. by temporarily suspending recruitment in study sites that are unable to meet the essential new expectations (e.g. the sites declare that they will not participate in remote visits, do not document the health status of clinical trial participants in the source documentation and in CRF).

2.6.4 Remote SDV- remote monitoring of source documentation

1. Pursuant to the latest EMA guidelines, remote monitoring of source documentation can be considered only during a public health crisis for studies involving the treatment or prevention of COVID-19 or in the final stages of data cleansing before database closure in key studies on major or life-threatening diseases without a satisfactory treatment option. The focus should then be on quality control of key data such as primary efficacy data and important safety data. Important secondary efficacy data can be monitored simultaneously, provided that this does not require access to additional documents and thus an increased burden on research site personnel.

The sponsor should determine the scope and nature of the remote SDV that he considers necessary for each clinical trial in this unique situation and should carefully consider the additional burden on the site. This is consistent with the recommendations presented in section 2.6.3 of Good Practice.

2. Site staff and monitors should be trained in the remote SDV process.
 - The investigator and research team should inform each study participant or designated legal representative about a new remote way of monitoring medical records and source data to ensure that he / she does not object to a remote review of his / her documentation for the purposes of the study and document this trial participant's medical records. If a trial participant objects to the remote verification of its documentation, remote verification (remote SDV) will not be performed for that trial participant.
 - Monitoring of remote source documentation (remote SDV) by the monitor can be carried out only in sites that provide secure internet connections, systems or platforms adequately protected against unauthorized access to data to avoid unauthorized viewing of the test participant's data.
3. If the agreed remote SDV process involves the use of videoconferencing and document review by the camera, ensure adequate transmission security and ensure data security:
 - The video quality should be adequate to allow reading without the risk of confusion between similar entries and to avoid adversely affecting the condition of conference call participants.
 - Video review of documents may include site staff sharing their computer screen on the monitor using a secure video conferencing application hosted on the computer. Video conferencing solutions in which data can be intercepted on third-country servers may not be acceptable.
 - Video review of documents requires a staff member to be present at all times to change the document being viewed or to scroll the document on the computer screen. Sponsors and Investigators should be aware of the importance of the burden that such SDV

methods can place on sites, therefore the review should be kept to a minimum of key data in key studies.

- Data transfers should be adequately protected against unauthorized access by third parties.
- 4. Performing remote verification of source documentation (remote SDV) should be established in agreement with the departments / divisions of QA, IT and legal in each organization to ensure compliance of the proposed technical solutions with the provisions on medical documentation and the protection of personal data of the clinical trial participant.

2.6.5 Restrictions on remote visits due to the availability of the site staff

1. Telephone conversations with the available staff members (e.g. "Site Crisis Contact Person – SCCP"), and an attempt to contact the Investigator
2. List of the most important issues to be addressed without unnecessary activities
3. (PG) Remote monitoring limited to critical data and processes (e.g. SAEs, AEs related to SARS-COV19, processes required to continue participation in the study)
 - Written summary of findings/ deviations after data review (CRF, listings, reports from vendor databases) and
 - possible telephone contact again if there are critical / serious findings
4. Regular reporting of contacts with the study sites
 - Extending the study team, e.g. temporary employment of a freelance clinical study coordinator, doctors of other medical specialties

2.6.6 On-site monitoring visit during the COVID-19 pandemic

If it is possible to conduct an on-site monitoring visit by the Clinical Research Monitor, it is recommended that the Monitor reduces its presence at the site to a minimum. To this end, combined, i.e. hybrid visits should be considered. Such visits consist of a remote visit and a site visit (on-site). This means that all activities related to monitoring of the study that can be performed remotely should be carried out during the remote visit, while the Monitor's presence at the site should be used for activities that can be performed only in the site (e.g. verification of patient source documentation, activities related to managing the investigational product)

2.6.7 Safety rules during the monitoring visit at the site during the COVID-19 pandemic

In order to conduct a monitoring visit, it is necessary to check the epidemiological situation and the possibility of conducting a visit to a specific site in safe conditions, in accordance with applicable GIS principles and recommendations. Many sites prepared their regulations regarding planning and conducting on-site visits. The study monitor should accept the applicable rules and notify the sponsor of the study of any restrictions.

Prior to the visit, the Study Monitor should provide a detailed list of necessary documents to be verified during the visit so that site staff can provide the documents in advance to the place where the Study Monitor will be.

It is recommended that the monitor only travels to the site only by its own car, avoiding public transport.

It is recommended that before entering the Site, a brief interview is conducted on the monitor's health status (including negative interview regarding the occurrence of shortness of breath, fever, cough) and possible contact with people suspected or suffering from Sars-COVID-19.

After entering the Site, the Monitor is obliged to maintain and respect the principles of safe distance and comply with current GIS guidelines regarding safe behavior during an outbreak of coronavirus, among others:

- disinfect hands with an appropriate formulation
- use personal protection equipment
- stay only in the space designated by the site
- restrict movement at the site and contact with the medical staff of the site
- strictly avoid contact with patients in the site

Additional visit to the place of storage, preparation of the drug / investigational product, the storage of laboratory kits and the place of performing Patient procedures (and thus the personal verification of drugs / investigational products, laboratory kits and other materials that are in these rooms) can be carried out only in justified cases after obtaining the consent of the Investigator and planning it accordingly the above rules.

The safety of patients and of the site's staff and study monitor should be paramount. Therefore, any deviations from the rules' application by the site's staff should be immediately reported to the Investigator, project manager, and to consider whether subsequent visits should take place at the site or only as remote visits.

2.6.8. Study conduct / CRA performance supervision

In the current situation, CRA performance quality control systems are also changed to adapt them to new conditions/ solutions introduced as alternative solutions.

1. It is necessary to ensure work standardization to guarantee quality of these new tasks performed by the study team.
2. Changing and adapting supervision plans for the monitoring processes (e.g. superior support during remote visits). Training of the monitoring team and superior.
3. Constant supervision of the line manager and project manager.
4. Securing substitute teams (back-up CRAs/ SWAT Team) in the project (redundancy plan) in the event of e.g. illness, quarantine, isolation without access to work tools such as the Internet / laptop

2.7 REPORTING STUDY PROTOCOL DEVIATIONS (PD)

2.7.1 Method of reporting PD due to difficulties in conducting the study caused by the COVID-19 epidemic, reporting to the URPL, Medicines Agency and/or bioethics committees

1. Reporting only those PDs that are associated with COVID-19 and affect the broadly understood patient safety and have a significant impact on the conduct of the study (in accordance with Article 37y Pharmaceutical Law)
2. In justified cases (provided that immediate safety measures are implemented within the meaning of Art. 37y of the Pharmaceutical Law (or Art. 51 of the Act on Medical Devices) comply with the definition of a substantial change), notification to the President of URPL and the BC, the changes introduced as a protocol amendment may take place after the occurrence of changes.
3. PD reporting concerning participant's safety does not change, while PDs related to COVID-19 will be reported in separate notification to the URPL / BC after an analysis by the sponsor. PDs which do not meet the reporting criteria in the mode provided in art. 37y Pharmaceutical Law (or Article 51 of the Act on Medical Devices), may be presented to the President of URPL and BC in separate communication after the pandemic has ended or as part of the report on conducting the study referred to in Art. 37 § 5 of Pharmaceutical Law
4. The sponsor's decision regarding significant deviations from the protocol is important. Prospective waivers of e.g. inclusion criteria are not accepted. It remains to be confirmed whether patients in screening who cannot have all study procedures performed in accordance with the study protocol and the verified criteria owing to COVID-19 remain to be classified as patients with screening failure with a re-screening option; the COVID-19 pandemic situation cannot be regarded as an excuse for violating the protocol criteria and compromising patient safety and well-being

2.7.2 How to report PD in the sponsor's internal systems

1. Follow the guidelines of the Sponsor, EMA and FDA to correctly assess PD in terms of the underlying causes: COVID-19 and non-COVID-19 PD and correct coding in systems as expected by EMA (opinion of 19 Mar 2020); the sponsor escalates and manages protocol deviations resulting from COVID-19 in accordance with its standard procedures; definition of PD and the gradation of deviations remain unchanged
2. Protocol amendments and mitigation of data integrity risks may be required by properly documenting the reasons and specifics of the deviations (EMA / FDA); regulatory authorities are of the opinion that it is permissible in this global situation to report and implement amendments to the protocol post factum. Regulatory authorities and sponsors do not allow prospective waivers from the study protocol. Deviations are reported in the agreed PD lists as part of a given study protocol
3. Balanced risk, exclusion of some data from SDV and SDR, relying on PD identification based on data entered into CRF without SDV / SDR

2.7.3 PD and inspections / audits

1. It is proposed to exclude some data from the qualitative assessment process during inspections or to change the approach to classifying potential findings for data collected

during the pandemic; as expected by the EMA (opinion of 19 Mar 2020) GCP inspectors should take a proportionate approach to protocol deviations reported for the period affected by the pandemic, and when such deviations are reviewed during the inspection, their classification should take into account the investigator and sponsor efforts to mitigate the participant's risks and to secure their best interests; an increase in deviations from the protocol in a COVID-19 situation will not in itself trigger any actions required under GCP § 5.20. However, they should be evaluated and reported in the clinical trial report in accordance with ICH E3

2. Exclusions of some data from the qualitative assessment process and postponements of inspections and audits caused by the global situation may be considered - other audit forms may be proposed (e.g. remote data inspection, analysis of documented central processes in off-site mode, analysis of sponsor reports (SMV, safety, reported PD) in order to meet the drug registration deadline

3. INVESTIGATIONAL MEDICINAL PRODUCT

3.1 MANAGEMENT OF THE INVESTIGATIONAL MEDICINAL PRODUCT

3.1.1 Delays in delivery of medicines to the study site

1. Constant monitoring by the sponsor / CRO of the situation related to the amount of IMP available at the study sites throughout the country
2. Ongoing contact with the IMP supplier to ensure operational continuity by identifying potential shortages on the supplier's side
3. Determining an alternative IMP supplier
4. Determining the mechanism of IMP transfer between study sites, if possible
5. Ensuring higher stock of IMPs at the study sites, increasing IMP availability

3.1.2 Patients cannot collect IMP at the study site

(e.g. due to quarantine, hospitalization in another study site, patient's decision, a ban on leaving home, problem with returning to the country)

1. Development of instructions on the practice and procedures for delivery of IMPs to the patient's home by the study sponsor / CRO in cooperation with the sponsor and the study site, including the transport conditions (documentation plus the conditions under which the IMP can be transported). You should consider cooperation only with courier companies operating in Poland
2. Verification of transport conditions in terms of courier safety to mitigate the risk of SARS-CoV-2 infection transmission (e.g. by providing procedures limiting courier-patient contact)
3. Appropriate designation of the drug prepared for transport (drug number, patient identification number). This is especially important when preparing IMPs for collection by several patients from the same study site
4. The development of a procedure by the study site adapted to the capabilities of the study site and the properties of the medicines used in the study (e.g. medical transport of the study site, collection by a family member of a patient or a designated person; this process needs to be properly documented). Always take into account the approved IMP storage and transportation specification prepared by the manufacturer
5. If the IMP is to be collected by a person designated by the patient - confirm with the patient the identity of the person designated by the patient, identify the designated person before dispensing the IMP, inform the patient about telephone confirmation with the site staff that the patient has received the medicine
6. Each time confirm with patients the possibility and method of delivery of the IMP to the patient's home. Before shipment and confirmation of receipt of the medicine. The patient should start taking the medicine only after confirming with the site staff that the correct medicine has been delivered (compliance with the assignment in the IVRS / IXRS system or any other automatic system)
7. It is necessary to document how the medicine is delivered to the patient's home in the medical records
8. For patients who are outside the country - arrange delivery of medicines to the patient's whereabouts or transfer the medicine from the nearest study site in a given country, if

possible take into account the process of obtaining an authorization for import of the IMP, if applicable

3.1.3 Site staff cannot dispense IMP to a patient

(study site closed, study sites transformed into infectious hospitals, staff absent because of child care, quarantined staff, infected staff)

1. Delegation of tasks between medical staff, within the legal framework, to ensure a replacement
2. Adding people to the site staff, taking into account the necessary training in the study procedures and appropriate documentation of the role of the additional staff and tasks delegated to them
3. Checking the possibility of using an alternative location / satellite study site

3.1.4 Difficult access to the IMP at the study site

(restrictions on drug access at the study site, short expiry date of the drug inventory)

1. Monitoring of the drug stock available at the study site by dedicated staff and immediate communication of shortages. As far as technically practicable and in cooperation with the sponsor / CRO managing drug allocation, rationalization of drug use with the shortest expiry date in the first place
2. Sponsor should explore the possibility of extending the drug's expiry date and adding an additional label with the updated the expiry date (relabelling) by trained site staff
3. Arrangement with the sponsor of the study to increase the supply of IMP

3.1.5 Access to other than investigational medicinal products (non-IMP / SoC)

(inability to provide other than investigational medicinal products / rescue medications, limited availability of such medications at wholesalers, interruptions in pharmaceutical wholesaler operations)

1. Creating a mechanism for the purchase of marketed medications or rescue medications used in the study by patients at a pharmacy and ensuring cost reimbursement to patients
2. Creating the possibility of non-cash settlements between the pharmacy and the study site and refunding these purchases to the study site by the sponsor

3.1.6 IMP handling depending on pharmaceutical form and route / method of administration of *(drugs that must be administered by medical staff, the need to assess the patient's health status before and after administration of IMP)*

1. Checking the requirements for technical conditions and equipment necessary for proper preparation of the drug for administration. In addition, checking the conditions necessary for proper administration of the drug to patients and legal requirements regarding the handling of a given class of drugs (e.g. safe handling of cytostatics, even in the oral form, which are treated as hazardous substances, requiring appropriate handling, storage and disposal - practically eliminating the possibility of sending and administering such treatment at the patient's home)
2. Checking the possibility of drug self-administration by patients in parenteral (non-intravenous) form

3. Delegation of an authorized person from the study team (e.g. nurse, co-investigator), with the required precautions to ensure the safety of both the patient and the delegated person, to administer the medicine as part of a home visit, after obtaining the patient's consent for such a procedure by phone and with appropriate documentation in the medical records
4. Appropriate preparation of the drug to be administered at the patient's home in accordance with the study specification and ensuring transport of the drug in accordance with the manufacturer's instructions. Each step should be documented in the patient's medical records
5. Checking the possibility of performing laboratory tests at a local laboratory if necessary before administering the drug
6. Checking the possibility of hiring external nursing staff to administer the study drug at the patient's home - Patient Concierge

3.1.7 Return of the drug

(collection of unused medicines and empty packaging at patient's home/ study sites)

Organizing the collection of medicines from patients and delivery to the study site using the drug supplier. If this is not possible, leaving unused medicines / packages at the patient's until the site visit

3.1.8 Documenting deviations from the study protocol

1. Ongoing documentation of any study site activities other than the study procedures (if applicable – approved by regulatory authorities, e.g. Office for Registration of Medicinal Products or Main Pharmaceutical Inspectorate and the bioethics committees)
2. Review of such deviations by the study monitor, documentation of deviations in visit / telephone contact reports
3. Establishing a procedure for reporting deviations from protocols to regulatory authorities and bioethics committees, if applicable

3.1.9 Infringement of patient personal data

(improper procedures for dispensing medicine to patients via third parties)

Developing the procedure and making sure that the courier / drug supplier will not provide patient identity data to the sponsor / CRO

4. DATA RELIABILITY

4.1 CRITICAL DATA FOR THE SAFETY OF STUDY PARTICIPANTS

4.1.1 Prioritizing key safety data

Identifying key study data relevant for the safety of study participants. These data should be given absolute priority over other data in terms of data collection, entry to CRF and review/monitoring. Examples of priority data may include data on SAE, adverse reactions of investigational medicinal product, inclusion criteria, IMP compliance, tolerance and efficacy assessments, and IMP safety and quality.

4.2 CRITICAL DATA FOR COMPLETION / PERFORMANCE OF THE STUDY

4.2.1 Decisions regarding key data for study projects - study continuity at risk, safety analyses, final data analysis

Identification of possible critical points and clinical study data necessary to secure study continuation and completion, and then determining the MINIMUM necessary measures to continue / complete the clinical trial, if possible, without compromising the safety of participants or other stakeholders (sites study teams, monitors etc.).

4.3 DATA - CONTINUITY

4.3.1 Identifying priority tasks in reduced study teams

Ensuring the continuity and good quality of entering key data by enabling competent staff members to work at study sites, and, if necessary, by providing assistance (e.g. by monitors) in remote training and obtaining authorization for new members of the site staff. Continuous entry of key data into CRF is necessary to enable central / remote supervision over the safety of clinical trial participants and the clinical trial.

4.4 DATA - GAPS

4.4.1 Risk of incomplete data followed by difficulties in identifying and justifying missing data

All visits of participants that have not taken place as well as study procedures and assessments that have not been carried out should be clearly documented and reported as such in CRF. It should be clearly described which data has not been obtained or is incomplete due to the pandemic.

4.5 DATA - DOCUMENTING ADDITIONAL OR EXTRAORDINARY MEASURES

4.5.1 Taking extraordinary measures and involving new people and parties (e.g. procedures carried out at other locations, remotely or at the patient's home, IP delivery, local laboratories, staff substitutions, etc.) may result in documentation gaps and difficulty in tracking the study activities; data obtained in such conditions may not meet the sponsor's requirements

In parallel with the new procedures, rules should be created to document them (e.g. defining necessary data/information range, responsible persons, document templates, etc.). Agreeing with the sponsor / validating procedures and suitability of data obtained in a non-standard way (e.g. local laboratories). Staff training.

4.6 DATA - QUALITY ASSURANCE

4.6.1 Limited access to study sites - no source documents can be verified on site

1. Remote data review / verification procedures:
 - Temporary, alternative quality and data consistency check procedures introduced with the knowledge and consent of the sponsor may include remote (telephone and videoconference) monitoring visits, increased involvement of central monitoring and data analysis, remote reviews and verification of source documents.
 - NOTE - the process of remote verification of source data e.g. by sending pseudonymised pdf files is not accepted by the EMA as it is too burdensome for the study sites - hence it should be limited to critical situations for patient safety, and not used as a replacement for routine data verification (resources of the study sites that would have to be used for this purpose should rather be allocated to continuous best-quality data entry and to other forms of contact with study monitors). Please see chapter 2.6, point 5.
2. If it becomes necessary to implement alternative data verification procedures in certain situations, this needs to be approved by the principal investigator who confirms that the study site has the necessary resources without placing too much burden on the site staff (it may be necessary to limit the scope of procedures to critical data)
3. Consideration shall be given as to whether to obtain from the study participants additional consent for data processing in a different way from that described in the initial consent and to verify their data - while the form of obtaining such consent during the pandemic may be different than the standard one.
4. During telephone / videoconference visits, the monitor can verify the documentation indirectly, e.g. by asking the site staff to read a fragment of source documentation and compare the read contents with the accessible CRF data.
5. If the selected method of alternative data verification for reasons of patient safety is to send documentation for review outside the study site - certified copies of key source documents can be transferred to monitors only in a secure manner, with blinded personal data of the study participants. Non-pseudonymised source documentation should not leave the site.
6. Copies sent for verification should be blinded in terms of all data allowing identification of the study participant (e.g. name, surname, PESEL, address, hospital book number, full date of birth, signatures, data of relatives, legal guardians, etc.). These copies should be certified for compliance with original documents and should bear the participant's study number on each page.
7. The monitor should control the process of data blinding in the documents received and in case of any shortcomings, the monitor should promptly indicate irregularities, correct the activities of the site staff and ensure effective and safe destruction of each copy of unblinded documents (including e.g. from inbox, sent and deleted email correspondence).
8. The documentation reviewed in such a manner should not be considered as verified, and the final verification of the source data should take place as soon as possible in accordance with the monitoring plan at the study site by comparing the data with the original source records.

9. Remote data review process should be documented along with detailed enumeration of the source documents being reviewed.

4.7 DATA - CONFIDENTIALITY

4.7.1 Risk of disclosure of personal and sensitive data resulting from the implementation of extraordinary procedures

It is necessary to include the issue of confidentiality of personal data in the planning of alternative procedures (provision / control / filtering / corrective actions, orderly and planned process of securing / destroying copies of documents). Confidentiality training in new procedures for all parties involved (e.g. site staff, monitors, third parties). Considering the need to obtain additional participant consent for new areas of data processing / sharing, including a simplified / remote form of such consent. Please see chapter 2.4.

4.8. BACKLOGS IN DATA ENTRY AND VERIFICATION

4.8.1 Increasing delays in obtaining, entering and verifying data in the current circumstances may cause long-term backlogs affecting the quality of data, but also the quality of supervision of the study and the safety of study participants

A data entry and review plan that also includes lower priority data and can be implemented on a larger scale and for longer. Possible measures include increasing the share of central monitoring, developing a plan and estimating the time frame to address the backlogs after the pandemic - modifying study operational plans (e.g. limiting the scope of reviewed data to the key data, risk based monitoring, multi-day and team monitoring visits), staff shifts (additional persons entering and verifying data), temporarily increasing the space available for monitoring at the study sites, etc. It may be helpful to agree on a simplified entry of some data - e.g. patient visits which took place (date of visit) and did not take place (not done) - this would facilitate tracking the course of the study at the affected study sites and estimating the size of possible backlogs in entering and verifying data without placing excessive burden on the site staff.

5. CONTACT DATA

If you have any questions about the recommendations or any other queries to which you did not find the answer, as well as suggestions or comments, please contact us.

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