Regulatory Express\_\_新冠疫情下的临床试验：来自MHRA, EMA,FDA的指导原则

“自3月以来，MHRA, EMA和FDA均针对新冠疫情下如何开展临床试验发布指导原则，并在近期予以了更新。三家监管机构的指导原则虽在具体内容上各有侧重但无出入，且基本原则高度一致，可以概述为：

* 受试者的安全性至关重要，参与试验的风险，特别是由于COVID-19带来的额外挑战，应该与试验可能带给受试者和社会的预期收益相权衡
* 应该很好地平衡疫情下试验流程的调整措施，特别应考虑到研究中心的合法权益，以避免COVID-19大流行期间在时间和人员配备方面造成进一步的负担
* 不接受对方案的前瞻性豁免

本期Regulatory Express将对上述指导原则中针对目前正进行中的临床试验给出的建议根据以下方面进行归纳汇总，便于大家查阅，推荐点击文末链接，查看原文。

1. Ongoing trials
2. IMP distribution
3. Informed consent
4. Monitoring
5. Auditing
6. Protocol deviation
7. Reimbursement of exceptional expense
8. Safety report and submission
9. Risk assessment & documentation
10. CRF & CSR
11. Communication with sites/IRB/authorities
12. Policies and procedures development

~~~~~~~~~~~~~~以下正文，主体~~~~~~~~~~~~~~~

1. Changes to ongoing trials

EMA

* + Conversion of physical visits into phone or video visits, postponement or complete cancellation of visits to ensure that only strictly necessary visits are performed at sites
	+ A temporary halt of the trial at some or all trial sites
	+ Suspension or slowing down of recruitment of new trial participants
	+ Extension of the duration of the trial
	+ Postponement of trials or activation of sites that have not yet been initiated
	+ Closing of sites. This should be done without compromising safety and well-being of patients already participating and data validity
	+ Transfer of participants to investigational sites away from risk zones, or closer to their home, to sites already participating in the trial, or new ones could occur. Initiation of new trial sites is generally not expected in the current situation unless no other solution exists for the trial participant
	+ If there is an urgent need to open a new trial site for critical trial visits for example outside the hospital, this may be implemented as an urgent safety measure (USM) first, with a substantial amendment (SA) application submitted later as for the approval and initiation of an additional site later
	+ Laboratory, imaging or other diagnostic tests are done at a local laboratory (or relevant clinical facility for other tests) authorised/certified (as legally required nationally) to perform such tests routinely (e.g. blood cell count, liver function test, X-ray, ECG etc.)
	+ Local analysis can be used for safety decisions. If this is a trial endpoint and the samples cannot be shipped to the central lab, analysis should be performed locally and then explained, assessed and reported in the clinical study report following ICH E3

MHRA

* + Using phone calls instead of protocol-directed in-person study visits is acceptable where possible
		- This will not constitute a serious breach of the protocol. A substantial amendment to update the protocol will not be required
		- We would however expect that any protocol deviations are well documented internally
	+ If participant monitoring visits need to be reduced due to COVID-19, this will not require a substantial amendment. However, do please ensure that your risk assessment and rationale is appropriately documented

FDA

* + Sponsors should evaluate whether alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment, including local labs or imaging centers) could be implemented when necessary and feasible, and would be sufficient to assure the safety of trial participants
	+ Sponsors should determine if in-person visits are necessary to fully assure the safety of trial participants (for example to carry out procedures necessary to assess safety or the safe use of the investigational product appropriately) in making the decision to continue use or administration of the investigational product, the sponsor should consider whether the safety of trial participants can be assured with the implementation of the altered monitoring approach
	+ In some cases, trial participants who no longer have access to investigational product or the investigational site may need additional safety monitoring (e.g. withdrawal of an active investigational treatment)
	+ The need to put new processes in place or to modify existing processes will vary by the protocol and local situation. For example, this assessment could include consideration of whether it is appropriate to delay some assessments for ongoing trials, or, if the study cannot be properly conducted under the existing protocol, whether to stop ongoing recruitment, or even withdraw trial participants
	+ COVID-19 screening procedures that may be mandated by the health care system in which a clinical trial is being conducted do not need to be reported as an amendment to the protocol even if done during clinical study visits unless the sponsor is incorporating the data collected as part of a new research objective

归纳总结

关于在研试验的变化：

基于风险/获益评估，在确保受试者安全和权益的前提下，对试验开展和相关流程可做以下调整：

* + 暂停试验，暂停入组，暂停启动，关闭中心
	+ 暂停受试者的试验药物治疗，受试者退出试验
	+ 考虑对长期无法用药或随访的受试者进行额外的安全监测
	+ 减少或延迟或取消受试者随访
	+ 受试者到远离危险区或离家近的研究中心进行随访
	+ 若需要开启新的研究中心以完成重要的访视，EMA允许按照“紧急安全措施”（USM）先行实施，随后向监管部门和伦理委员会提交实质性的方案修正申请
	+ 采用电话、视频等方式进行远程随访
	+ 在当地医院进行安全相关检测，其数据可用于安全性分析
	+ 疗效终点指标的检测若无法在中心实验室完成，在当地实验室进行检查的结果可用于疗效评估，但此情况需要在研究总结报告中予以说明
	+ 受试者应医疗卫生系统要求所作的COVID-19相关筛查不需对方案进行修正，除非出于研究目的需要收集该数据
1. Changes to the distribution of the IMP

EMA

* + The following measures could be considered provided that they do not create shortages of marketed medicinal products:
		- Larger amounts of trial medications than normally foreseen can be provided to the participant (in particular IMP, when prepared specifically for the purposes of the trial). This may be done providing that the continuation of treatment is under adequate supervision of the responsible investigator
		- It is recommended for all IMPs and non-IMPs in clinical trials that appropriate stock is maintained to ensure treatment in case of distribution failure
	+ Re-distribute the IMP between sites
		- Should follow GMP annex 13
		- should only be considered in cases where a direct distribution of the IMP to a trial site by the usual distributor is not possible or in the exceptional circumstance where a trial participant is transferred from one site to another
		- Should assess whether sites can handle and control such a re-distribution process, especially in case of restricted conditions for storage
		- Should follow a written procedure established in cooperation with the Qualified Person or the person responsible for distribution of the IMP
		- Sites should be provided with sufficient information to ensure that the process can be performed securely
	+ Direct delivery to patients (DTP）
		- The delivery is generally expected to happen from investigator sites (e.g. via hospital (or other) pharmacies as applicable) to trial participants
		- If direct from sponsor to trial participant
			* The sponsor should check the National Competent Authority （NCA）guidance regarding the possibility of direct sponsor to trial participant shipment, as it is likely that such measures can only be implemented under specified conditions (e.g. agreement with sites, dedicated couriers with procedures to only allow delivery directly to a trial participant or his/her career, solid shipment and receipt procedures, informed consent provisions if necessary for the sponsor’s third party to handle personal information etc.), and for a limited period

MHRA

* + Delivery of IMP to a patient’s home is acceptable and no substantial amendment notification to the MHRA will be required
	+ Participants must consent verbally (and this should be documented in their notes) to providing contact details for shipping purposes
	+ If the participant does not want to sign for the delivery due to self-isolation, then a follow up phone call could be used to confirm they have received the package
	+ The sponsor should also consider if any training is required for administration of the IMP
	+ Further consideration to DTP:
		- * Storage requirements
			* whether the medicine has any specific storage requirements, and how those are managed during posting
			* What assurance can be given about the integrity of the product during transit, for example should a temperature monitoring device be used
			* The stability of the product and margin of safety: for example a product with a very stable profile at temperature extremes would require less monitoring than one with a narrow stability range. The expiry of the product may need to be shortened if is delivered in ambient temperature
		- Delays in posting
			* Potential to affect continuity of supply
			* Shortage of the medicine
		- Medicine accountability
			* The mechanism for confirming that the subjects have received the IMP, and it has not been delivered to someone else
			* Whether the medicine needs to be signed for and sent by courier or recorded delivery
			* Whether there needs to be a follow-up call to the subject

归纳总结

关于试验药品的发放的变化

* + 在不引起市场药品供应短缺的情况下，可考虑：
		- 向受试者提供比通常预计的更多的试验药物（尤其是以试验为目的的在研药物），前提是保证继续治疗是在研究者的监督下进行。
		- 建议保证所有IMP 和 non-IMP的适当库存
	+ 接受从研究中心通过邮寄/快递方式向受试者发药
	+ 由申办者直接向受试者发药需确认符合相关条件，如：与研究中心的协议，快递条件和程序等
	+ 应与配送试验药品的人员建立和遵循书面流程
	+ 通过邮寄/快递方式向受试者发药涉及将受试者的个人信息告知给邮寄/快递人员的情况，需获得知情同意。若采取口头知情，研究者需记录相关知情同意过程
	+ 需考虑是否有必要向受试者提供相关药物使用的培训
	+ 邮寄/快递方式发药还需考虑
		- 药物的储存要求
		- 可能出现的延迟送达风险
		- 药物清点，应有机制确认受试者接收了药物
1. Changes to Informed consent

EMA

* + The following specific aspects should be taken into account with trials involving COVID-19 patients
		- If written consent by the trial participant is not possible (for example because of physical isolation due to COVID-19 infection), consent could be given orally by the trial participant (Art 2(j) of Directive 2001/20/EC) in the presence of an impartial witness. In such cases, the witness is required to sign and date the informed consent document and the investigator is expected to record how the impartial witness was selected
		- In addition, it could be considered that the trial participant and the person obtaining consent sign and date separate informed consent forms. In either case, all relevant records should be archived in the investigator site’s Trial Master File. A correctly signed and dated informed consent form should be obtained from the trial participant later, as soon as possible
		- In case of acute life-threatening situations, where it is not possible within the therapeutic window to obtain prior informed consent from the patient (or her/his legal representatives(s)), informed consent will need to be acquired later, when this is allowed in national legislation. In these cases, the investigator is expected to record why it was not possible to obtain consent from the participant prior to enrollment
	+ Avoid the need for trial participants to visit investigator sites for the sole purpose of obtaining re-consent. If re-consents are necessary for the implementation of new urgent changes in trial conduct (mainly expected for reasons related to COVID-19), alternative ways of obtaining such re-consents should be considered during the pandemic e.g. contacting the trial participants via phone or video-calls and obtaining oral consents supplemented with email confirmation. Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the trial participants will be back at the regular sites
	+ Any validated and secure electronic system already used in the trial for obtaining informed consent can be used as per usual practice and if in compliance with national legislation

MHRA

* + Subjects must consent to any sharing of their personal information outside the trial site

FDA

* + In all cases, it is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them

归纳总结

关于知情同意的变化

* + 因疫情影响而对试验流程及随访而作的调整或变更必须告知受试者
	+ 若需将受试者个人信息告知研究中心以外人员时，应获得受试者的同意
	+ 疫情期间对于知情同意书的变更，可采取电话或视频告知受试者，以获得其口头同意以及邮件确认的形式完成。上述知情同意过程应予以记录，并在受试者能返回研究中心访视时即完成知情同意书的签署
	+ 若试验先前已采用电子知情同意的方式，且该方式确认可靠合规，则可继续采用该方式
1. Changes to monitoring

EMA

* + Cancelling of on-site monitoring visits and extending of the period between monitoring visit
	+ Implementing phone and video visits (without unnecessarily increased burden to the investigator site and taking into account trial participant integrity)
	+ Adapting the on-site monitoring plan when it is impossible to follow, supplementing it with (additional/increased) centralised monitoring and central review of data if possible and meaningful
	+ Results of adjusted monitoring/review measures should be reported to the sponsor in monitoring reports and in the clinical study report
	+ It is essential that robust follow-up measures are planned and ready to be implemented when the situation is normalised. This should likely include increased on-site monitoring for a period that is sufficient to ensure that the impact of the reduced monitoring could be rectified and problems resolved or properly documented for reporting in the clinical study report
	+ Remote SDV
		- So-called remote source data verification (e.g. providing sponsor with copies of medical records or remote access to electronic medical records) is currently not allowed in most member states as it might infringe trial participants’ rights. In addition, provision of redacted/ de-identified pdfs files will not be acceptable as it puts disproportionate burden on site staff
		- Temporary solutions related to remote access and conditions for such, providing that methods can be used that restricts access to trial participant records, in line with the principles of necessity and proportionality. This should however also be clarified with other relevant authorities in this area (such as, without limitation, Ethics Committees and data protection agencies) and is consequently not allowed unless a member state has given specific guidance allowing this
	+ MHRA Remote monitoring
		- Direct access to patients EHR (Electronic Health Record) away from the site creates issues around confidentiality. Consider where this access takes place, for example will CRAs (Clinical Research Associates) be accessing records in an open plan office, public space or other location where others who are not authorised could view sensitive information
		- Trial participants will need to consent to any identifiers leaving the site and be assured that their confidentiality will be protected
		- It is likely that there will be increased pressures on clinical staff during this period, so it is important to make sure that extra burdens are not placed on investigators around scanning and uploading many documents
		- The use of alternative means of oversight such as teleconferences and/or videoconferences is encouraged

FDA

* + Remote monitoring
		- If planned on-site monitoring visits are no longer possible, sponsors should consider optimizing use of central and remote monitoring programs to maintain oversight of clinical sites

归纳总结

关于监查的变化

* + 可取消监查或减少监查频次
	+ 若无法进行实地监查，可采用中心和远程监查的方式
	+ 监查方式的调整应在监查报告和研究总结报告中予以体现
	+ 监查员远程登陆EMR进行SDV应考虑确保隐私信息的保密，确认其合规性
	+ 若受试者的个人信息会在研究中心以外被人获及，则需获得知情同意，并确保隐私信息得到保护
	+ 考虑到会增加研究者和研究工作人员的工作负担，不建议将原始文件隐去受试者个人身份信息后以扫描或图像方式发给监查员供其进行SDV
	+ 鼓励电话会议或视频会议的方式
	+ 应有计划在局势好转后采取强有力的措施，如增加监查频次以确保前期积累的问题得以纠正、解决和记录
1. Changes to auditing

EMA

* + Audits should in general be avoided or postponed and should only be conducted if permitted under national, local and/or organizational social distancing restrictions
	+ For critical trials, on-site visits as well as remote audits can be considered, after agreement with the investigator and if the audits are assessed as essential, e.g. triggered audits with the purpose of investigating serious non-compliance

归纳总结

关于稽查的变化

* + 一般而言应考虑暂停或推迟稽查工作，除非在地区，国家或组织机构的社交距离限制允许的情况下进行
	+ 对于关键试验，在与研究者达成一致且稽查被认为是必要的（如严重违规触发的稽查），可考虑采用现场以及远程方式进行稽查
1. Protocol deviation

EMA

* + An increase in protocol deviations in relation to the COVID-19 situation will in itself not trigger the actions required by GCP § 5.20. They will however need to be assessed and reported in the clinical study report, following ICH E3
	+ Sponsor escalates and manages such protocol deviations in accordance with their standard procedures

MHRA

* + There will be an increase in protocol deviations; please ensure they are well documented, to enable appropriate evaluation for the trial
	+ An increase in protocol deviations in relation to Coronavirus will not constitute a serious breach, therefore there is no need to report this to us (unless of course patients are being put at risk)

归纳总结

关于方案违背

* + 因疫情造成方案偏离的增加，不属于GCP § 5.20 中所界定的违规范畴
	+ 申办方应依据标准流程对方案偏离进行上报、管理和记录
	+ 遵循ICH E3在研究总结报告中对疫情相关的方案偏离进行评估
1. **Reimbursement of exceptional expense**

EMA

* + If, in order to implement urgent measures for the protection of participants involved in a clinical trial, expenses may arise which may be borne initially by the participants, these should typically be compensated subsequently by the sponsor via the investigator

归纳总结

特殊费用的报销

* + 出于保护受试者的目的而采取的紧急保护措施所产生的先由受试者自行支付的费用，应由申办者通过研究者给予受试者补偿
1. **Safety reporting & Safety report submission**

EMA

* + It is important that the investigator continue collecting adverse events from the participant through alternative means , e.g. by phone
	+ Sponsors are expected to continue safety reporting in adherence to EU and national legal frameworks

MHRA

* + SAE reporting: Deviation from protocol defined timelines in this case does not require a substantial amendment to MHRA
	+ Particular attention should be paid to timely reporting of suspected unexpected serious adverse reactions (SUSARs) which put participant safety at risk on a trial or have the potential to impact participants of other trials. Every effort should be made to notify MHRA in this case

归纳总结

安全报告和安全报告的提交

* + 研究者应采用其他方式，如电话，继续收集受试者的不良事件信息
	+ 申办方应继续遵循相关法规进行安全报告
	+ 因疫情造成SAE上报时限超出方案规定的时限，不需要作为实质性修正上报MHRA
	+ 可能影响受试者安全的SUSAR应及时上报MHRA
1. **Risk Assessment & Documentation**

EMA

* + It is expected that the sponsor performs a risk assessment of each individual ongoing trial and the investigator of each individual participant and implements measures which prioritise subject safety and data validity. In case these two conflict, subject safety always prevails
	+ It is important that sponsors in their risk assessment consider prioritisation of critical tasks in the clinical trial and how these are best maintained
	+ These risk assessments should be based on relevant parties’ input and should be documented on an ongoing basis
	+ The sponsor should reassess risks as the situation develops. This reassessment should also be documented
	+ It is possible that with the escalation of the pandemic, local circumstances lead to a local change in risk assessment, therefore the need to implement additional measures may arise, and an investigator-driven risk assessment might be necessary (and communicated to the sponsor)
	+ Regarding participants enrolled in ongoing clinical trials who may be determined as being a risk group for COVID-19 or who are in trials involving treatments, which may increase such risk, the potential impact of COVID-19 on these participantgroups should be carefully considered when deciding to start or continue such trials

MHRA

* + Brief risk assessment and documentation of the impact of this (*refer to changes to the conduct of trials*), with consideration of prioritisation of critical activities such as safety reporting

FDA

* + Sponsors and clinical investigators should document the reason for any contingency measures implemented
	+ Sponsors and clinical investigators should document how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted

归纳总结

风险评估和记录要求

* + 申办者应对每个正在进行的试验进行风险评估，研究者应对每个受试者进行风险评估。采取的措施优先考虑受试者安全和数据有效性，两者冲突时，以受试者安全为重
	+ 申办方的风险评估应首先考虑试验的关键任务以及如何最好地得以实施
	+ 风险评估应基于各方意见，并应持续记录。情况变化时应重新进行评估并记录
	+ 随着大流行的升级，当地风险评估随当地情况变化而变化，因此可能需要采取额外的措施，也可能需要研究者主导进行风险评估（并于申办者沟通）
	+ 对于受试者，可能属于疫情下的高危人群，或是正在进行的试验治疗可能增加其感染风险，因此需要仔细考虑COVID-19对这些受试者的影响，决定是否继续试验
	+ 申办者和研究者针对疫情对试验的影响以及相关调整措施的风险评估应做好记录
	+ 申办者和研究者应记录疫情导致的调整或变化，以及这些变化持续的时间，哪些受试者受到了影响以及具体的影响是什么
1. CRF & CSR

FDA

* + It will be important to capture specific information in the case report form that explains the basis of the missing data, including the relationship to COVID-19 for missing protocol-specified information
	+ Sponsors should describe in appropriate sections of the clinical study report (or in a separate study specific document)
		- Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 control measures
		- A listing of all participants affected by the COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual’s participation was altered
		- Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study

归纳总结

CRF & CSR

* + 应在病例报告表（CRF）中收集具体的信息，以此为基础对缺失的信息进行解释，包括与疫情的关系
	+ 申办者应在研究总结报告的合适部分或单独的文件中描述：
		- 在疫情下针对试验管理而采取的应急措施
		- 受到疫情影响的受试者列表，标注所在研究中心，描述每个受试者参与试验中具体哪些方面受到了疫情的影响
		- 分析和讨论实施的应急措施（例如，试验参与者终止研究产品和/或研究，用于收集关键安全性和/或有效性数据的替代程序）对研究报告的安全性和有效性结果的影响
1. **Communication with sites/IRB/authorities**

EMA

* + Agreement with and communicate to site:
		- Changes to trial conduct should be agreed with and communicated clearly to investigator sites
		- Agreements may be documented as e-mail exchange
	+ In case the risk assessment leads to actions that affect the trial as described below in a) and b), the relevant competent authorities and Ethics Committees must be informed in accordance with the Directive 2001/20/EC and national laws:
		- a) When a new event is likely to have a serious effect on the benefit-risk balance of the trial, it is possible that immediate actions are required by the sponsor and investigator to protect the subjects against immediate hazard. These, urgent safety measures may be taken without prior notification, but the information needs to be provided *ex post* to the National Competent Authority (NCA) and the Ethics Committee as soon as possible (EC 2010/C82/01; 3.9)
		- b) If changes are likely to affect the safety or well-being of the participants and/or the scientific value of the trial, but do not require immediate action from sponsor or investigator, it should be possible to submit them as substantial amendment applications
	+ Even when a trial is put on hold for reasons not linked to participant safety (as covered by a) and b) ), e.g. to avoid unnecessary strain on health care professionals, the sponsor is expected to notify NCAs and Ethics Committees, unless national regulatory guidance instructs otherwise
	+ The impact of protocol changes on clinical data interpretability needs to be properly assessed by the sponsor and the overall evidence generation package could be subsequently discussed within scientific advice with regulatory authorities. A relevant guidance on the implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trial by the CHMP Biostats working party was published on March 25 2020

FDA

* + Sponsors and clinical investigators are encouraged to engage with IRBs/IEC as early as possible when urgent or emergent changes to the protocol or informed consent are anticipated as a result of COVID-19
	+ Such changes to the protocol or investigational plan to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19) may be implemented without IRB approval or before filing an amendment to the IND or IDE, but are required to be reported afterwards. FDA encourages sponsors and investigators to work with their IRBs to prospectively define procedures to prioritize reporting of deviations that may impact the safety of trial participants
	+ With respect to efficacy assessments, FDA recommends consultation with the appropriate review division regarding protocol modifications for the collection of efficacy endpoints, such as use of virtual assessments, delays in assessments, and alternative collection of research-specific specimens, if feasible
	+ If changes in the protocol will lead to amending data management and/or statistical analysis plans, the sponsor should consider doing so in consultation with the applicable FDA review division. Prior to locking the database, sponsors should address in the statistical analysis plan how protocol deviations related to COVID-19 will be handled for the prespecified analyses

归纳总结

与研究中心/IRB/官方的沟通

* + 疫情下采取的应急措施应与研究者/研究中心沟通、记录并达成一致
	+ 通过风险评估发现必须采取的措施对受试者的安全和权益或是研究的科学性有所影响，应事先上报监管部门和伦理委员会。除非是为了避免对受试者造成即刻危害而采取的紧急措施，可在采取措施之后尽快上报
	+ 如果暂停试验的原因并非由于受试者的安全性，如避免对医疗保健专业人员造成不必要的压力，期望申办者告知监管部门和伦理委员会，除非国家法规有另外的规定
	+ 申办者应评估方案变更对临床数据可解释性的影响，随后可与监管部门讨论和咨询其意见。 2020年3月25日，CHMP Biostats工作组发布了关于冠状病毒病（COVID-19）对正在进行的临床试验的方法学方面的影响的相关指南（参见Reference Link）
	+ 当预计因疫情影响将对方案或知情同意书进行紧急更改时，建议研究者和申办者尽早与伦理委员会联系
	+ 鼓励申办者和研究者与伦理委员会合作，事前确定影响受试者安全的方案偏离应采取优先报告的程序
	+ 对于方案中疗效终点数据收集的相关修改，建议咨询审评部门
	+ 如果方案变更会导致修订数据管理和/或统计分析计划，申办者应考虑与审评部门协商后修改。 在锁定数据库之前，申办者应在统计分析计划中说明如何在预先规定的分析中处理与疫情相关的方案偏离
1. **Develop policies and procedures**

FDA

* + Sponsors, clinical investigators, and IRBs should consider establishing and implementing policy and procedures, or revise existing policy and procedures, to describe approaches to be used to protect trial participants and manage study conduct during possible disruption of the study as a result of COVID-19 control measures at study sites
	+ Changes to policy and procedures could address, but not be limited to, impact on the informed consent process, study visits and procedures, data collection, study monitoring, adverse event reporting, and changes in investigator(s), site staff, and/or monitor(s) secondary to travel restrictions, quarantine measures, or COVID-19 illness itself
	+ Policy and procedures should be compliant with applicable (regional or national) policy for the management and control of COVID-19. Depending upon the nature of the changes described above, a protocol amendment may be required under the applicable regulations

归纳总结

创建政策与流程

* + 申办者、研究者和伦理委员会应考虑制定相关政策和程序，或对现行的政策和程序进行修改，以描述疫情下对受试者的保护和研究管理采取的措施
	+ 需变更的政策和程序包括但不限于知情同意程序、研究访视和程序、数据收集、研究监测、不良事件报告等
	+ 政策和程序应遵循所在区域或国家发布的疫情下如何管理临床试验的建议和指导原则。根据上述流程变更的性质，可能需要根据适用的法规对方案进行修订

Reference:

EMA:

<https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf>

<https://www.ema.europa.eu/en/implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical-trials>

MHRA

<https://mhrainspectorate.blog.gov.uk/2020/03/12/advice-for-management-of-clinical-trials-in-relation-to-coronavirus/>

[https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19#submitting-paperwork-for-trials-which-have-been-halted](https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19)

FDA

<https://www.fda.gov/media/136238/download>