The reliability and integrity of overall survival data based on follow-up records only and potential solutions to the challenges

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Summary

Overall survival (OS) is considered the standard clinical endpoint to support effectiveness claims in new drug applications globally, particularly for lethal conditions such as cancer. However, the source and reliability of OS in the setting of clinical trials have seldom been doubted and discussed. This study first raised the common issue that data integrity and reliability are doubtful when we collect OS information or other time-to-event endpoints based solely on simple follow-up records by investigators without supporting material, especially since the 2019 COVID-19 pandemic. Then, two rounds of discussions with 30 Chinese experts were held and 12 potential source scenarios of three methods for obtaining the time of death of participants, including death certificate, death record and follow-up record, were sorted out and analysed. With a comprehensive assessment of the 12 scenarios by legitimacy, data reliability, data acquisition efficiency, difficulty of data acquisition, and coverage of participants, both short-term and long-term recommended sources, overall strategies and detailed measures for improving the integrity and reliability of death date are presented. In the short term, we suggest integrated sources such as public security systems made available to drug inspection centres appropriately as soon as possible to strengthen supervision. Death certificates provided by participants' family members and detailed standard follow-up records are recommended to investigators as the two channels of mutual compensation, and the acquisition of supporting materials is encouraged as long as it is not prohibited legally. Moreover, we expect that the sharing of electronic medical records and the legal disclosure of death records in established health registries can be realized with the joint efforts of the whole industry in the long-term. The above proposed solutions are mainly based on the context of China and can also provide reference for other countries in the world.

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Can we totally trust the validity of death time based solely on follow-up records in clinical trials ?

Randomised trials are a type of scientific study typically used to test new healthcare treatments. Overall survival (OS) is considered the standard clinical endpoint in randomised trials to support effectiveness claims in new drug applications, particularly for lethal conditions such as cancer, since it provides direct measures of true clinical benefit and can be easily, precisely and objectively measured.[1,2] Although the proportion of cancer drugs that are approved on the basis of surrogates has increased over recent years, OS remains the second most common primary endpoint after progression-free survival (PFS) and is frequently required for regular approval.[3,4] In recent years, studies on endpoints have mainly focused on the alternatively of surrogate endpoints over OS.[5–8] There were also some studies questioning and addressing the integrity of clinical trials, particularly since COVID-19.[9–12] However, the sources and reliability of OS collection in the setting of clinical trials have seldom been doubted and discussed.

Generally, reported data in registered trials should be accurate, complete, timely and verifiable from source documents.[13] Accurately obtaining and recording the date of death is critical to OS accuracy, given that pivotal trials for drug approval were found increasingly fragile.[14–16] In practice, there are three commonly-used and acceptable sources for the time of death in trials at present, including the death certificate provided by the participant's family, the death record from the hospital and the clinical follow-up record by investigators, which follows basically the same pattern with investigator-initiated studies.[17,18] There is a lack of unified standards for source identification of death in registered trials. The time of death acquired from death certificates and death records is generally considered to be highly reliable and to have no conflict of interest, but it is highly dependent on the cooperation of the participant's family members at the request of the investigators and the likelihood that the patient will die in a particular hospital, respectively.[19,20] Identifying time of death during regular clinical follow-up, which is still highly dependent on the compliance of participants' families, is the most common method, though the detailed proportion of death sources may vary among countries.

This phenomenon, however, raised our concerns and a straightforward question: can we totally trust the validity of death time based solely on follow-up records, which is generally unstructured documented by investigators in medical records for clinical trials according to notification from participants' families? After all, researchers have conflicts of interest regarding trial results to some extent, and sometimes the authenticity of clinical follow-up record cannot be verified by supervision agency through other reliable channels. Actually, cancer drug trials are among the most vulnerable to loss to follow-up due to the requirement for regular on-site visits for synchronizing multiple activities, such as tumour assessments, drug administrations and laboratory sample collection.[21] This is particularly the case during the COVID-19 pandemic, in which patient care is delayed and may cause withdrawal in advance.[12,13,22]

With subjects dropping out more frequently, the collection of death information is bound to be more incomplete. Trials may suffer from substantial power loss and underestimated treatment effect size, and if unbalanced loss to follow-up occurs different arms or regions, trials may have even poorer performance and be more fragile.[23,24] As we know, trial integrity and data quality are general principles emphasized by all regulatory authorities and critical issues faced by trials using OS as the primary endpoint.[25,26] These facts remind us that it is time for action to make every effort to sort out all potential ways, and to assess its pros, cons and barriers for acquiring the date of death in clinical trials, as well as updated follow-up data for patients who are still alive. This pertains not only to trials using OS but also to trials using other time-to-event endpoints covering death.

12 potential sources for the collection of death time

Herein, two rounds of expert discussions and meetings were held, in which 30 expert representatives from clinical research investigator and administrator, statistician, regulatory agency, ethics committee, sponsor, and lawyer were called together to sort out the potential scenarios for obtaining the time of death of participants in clinical trials. Additionally, five indicators, including legitimacy, data reliability, data acquisition efficiency, difficulty of data acquisition, and coverage of participants, were utilized to evaluate the advantages, disadvantages and barriers of each source. Legitimacy in this study specifically indicate whether data collection of death date of participants is legal at the time. All of the above indicators were classified into three categories, low, moderate, and high; legitimacy was divided into yes, no and depends. On this basis, both short-term and long-term recommended sources, overall strategies and detailed measures for improving the integrity and reliability of death date are delivered.

A total of 12 scenarios are sorted out as potential sources for the time of death of participants, including 5 scenarios based on death certificates sealed by authorized units, 4 scenarios based on death records registered in electronic systems owned by governments and hospitals, and the other 3 scenarios based on clinical follow-up records specific for trials (Table 1).

Potential source of time of death data	Legitimacy	Data reliability	Data acquisition efficiency	Data acquisition difficulty	Coverage of participants
Death certificate					
Scenario 1: Death certificate issued directly by primary medical institution	Yes	High	High	Low	Low
Scenario 2: Death certificate issued directly by other medical institutions	Depends	High	High	High	Moderate
Scenario 3: Death certificate provided by participant's family members	Yes	High	Moderate	Moderate	High
Scenario 4: Public death information, such as an obituary, provided by participant's family members	Yes	High	Moderate	Moderate	Low
Scenario 5: Death certificate issued directly by public security system	No	Moderate	High	High	High
Death record					
Scenario 6: Death record from primary medical institution	Yes	High	High	Low	Low
Scenario 7: Death record from other medical institution	Depends	High	High	High	Moderate
Scenario 8: Death record from civil registration system	No	Moderate	High	High	High
Scenario 9: Death record from vital registration system	No	Moderate	High	High	High
Follow-up record					
Scenario 10: Simple follow-up records without supporting materials	Yes	Low	Low	Moderate	High
Scenario 11: Detailed standard follow-up records without supporting materials	Yes	Moderate	Low	Moderate	High
Scenario 12: Detailed standard follow-up records with supporting materials	Depends	High	Low	Moderate	High

Note: Green indicates advantaged in this dimension, pink indicates disadvantaged and yellow indicates a moderate level.

Table 1: **Overview and evaluation of potential source scenarios for time of death.**

Undoubtedly, data reliability at the premise of legitimacy is what the regulatory agency values most, especially for the primary endpoint.[27,28] Although collecting death date including cause of death in high-income countries could easily and efficiently achieved through national vital registration system (Scenario 9) or civil registration system (Scenario 8), the recorded death date shall not be used for purposes other than population management and statistical analysis for the sake of privacy and security.[29–31] Acquiring death certificates issued by the public security system directly (Scenario 5) is constrained to immediate family members and qualified lawyers in China and beyond. These three paths are not expected to be open to investigators in the short term due to privacy protection; additionally, information in the above three paths are usually not updated in a timely manner to some extent. However, we strongly recommend them, especially for the public security system, which is open to drug inspection centres with appropriate restrictions, as a way to validate the accuracy of the death date provided, thus effectively promoting the reliability of evidence used for drug approval.

Overall, death certificates issued by medical institutions or deaths recorded in electronic medical record (EMR) systems (Scenarios 1, 2, 6, and 7) are deemed highly reliable and efficient sources for the time of death; however, the coverage of participants is low to moderate, as the issue of death certificates is determined by whether the participants died in hospitals.[32] If the participants died in other hospitals instead of the same hospital where they participated in the trials, the legitimacy of the death certificates or records from those other hospitals could be questionable. It is a violation of the Medical Practitioners Act for attending doctors or other medical professionals to privately inform sponsors or other doctors outside the hospitals of the death date.[33] The trial investigators could try to obtain the death information of participants who died in other hospitals through a shared EMR system between medical institutions on the premise that such sharing and access must be authorized by patients in advance.[34]

For the sake of maximizing data integrity, minimizing follow-up workload and facilitating clinical research, achieving the integration and sharing of EMRs at the largest scale is an ideally long-term strategy. With an increasing number of medical institutions joining the network, there is an opportunity to escalate the coverage of participants to a high level, thus making trials much easier. Globally, national patient EMRs have long been promoted by governments and healthcare systems increasingly, albeit to varying degrees across different countries.[35,36] Despite these potential benefits, great efforts and identified willing of patients, to share their data for a wide range of uses provided adequate

security safeguards,[37] great challenges were experienced in implementing large-scale EMR system.[38] The fundamental difficulties lie in establishing strong leadership, willingness and trust between hospitals, who are reluctant to share data without enough incentives, even though patients themselves are the actual owners of their health data.[39,40] Therefore, there has been no real breakthrough in data sharing between hospitals globally, although the issue has been discussed, and consensus on its importance was reached long ago.[41]

The other five scenarios (3, 4, 10, 11, and 12) all depend on the close relationship and cooperation of the participant's family members with the investigative team; thus, the difficulty of data acquisition ranks at a moderate level. Using public death information provided by family members is the last option among the five scenarios because the likelihood is not that high; that is, the coverage of participants is too low. Based on the comprehensive performance of the five indicators, we suggest that a death certificate provided by the participant's family members (Scenario 3) be the first choice, since it has the advantages of legitimacy, realizability, high coverage and acceptable difficulty in data acquisition, followed by detailed standard follow-up records with or without supporting materials (Scenario 11, 12) depending on the legal allowance of acquiring supporting materials and simple follow-up records without supporting materials (Scenario 10).

Follow-up records may play a central role in determining the time of death of participants in clinical trials, and some of the records are simple and uniform. The critical factors differentiating the ranking of Scenarios 10, 11, and 12 are data reliability and legitimacy. Given that obtaining supporting materials for a notification of death from the participant's family without informed consent, such as audio recordings and screenshots, may infringe upon the participant's privacy, it takes time for ethics committees and society to achieve a consensus on signing a prior notice with the participant's family at the appropriate time and in a legal manner in case of loss to follow-up. Despite being highly reliable, detailed standard follow-up records without supporting materials may take precedence over those with supporting materials at some circumstances at the time.

We should be fully aware that there is an opportunity to largely upgrade the reliability of death data by simply standardizing a more detailed follow-up record manner and format. Therefore, we make our recommendations for requirable items of standardized follow-up records of participants in trials, particularly when the primary endpoint is OS.

a) Follow-up date, accurate to the hour;
b) Follow-up mode, such as face-to-face chat, telephone chat, voice chat, text message, and email;
c) Basic information of follow-up personnel, including at least name and role in trial;
d) Basic information of the follow-up subject, including at least name, relationship with participant, and contact information;
e) Survival status of participant (living or deceased) (record f) item if the participant is still living, record g) item if the participant is deceased);
f) Physical condition of participant (good, poor, very poor);
g) Date of death, place of death (at home, at hospital), cause of death;
h) Self-evaluation of the reliability of follow-up information (high, moderate and low).

More importantly, the five scenarios (3, 4, 10, 11, and 12) are the most feasible and common sources of time of death in actual situations where access to death records and the sharing of EMRs are extremely limited, especially for Scenarios 3 and 10, although they are limited by the extent of the relationship between the participant's family members and the investigative team. On this basis, we strongly recommend that the investigative team make every effort under the patient-centred principle to improve the follow-up compliance of participants and their family members.

Strategies and measures recommended for promoting follow-up compliance in trials

To improve the ecosystem as a whole, we perceived four major strategies could make a difference in trial compliance (Fig. 1). Among them, building sound doctor–patient relationships and fostering a positive perception of clinical trials at a societal level are two fundamental strategies that require massive systematic social engineering.[41–43] In recent years, particularly since COVID-19 started spreading in the ending of 2019, the promotion and application of remote electronic tools to capture clinical outcomes have achieved rapid and substantial progress globally.[44–48] Further promoting innovative tools to make follow-up more convenient is undoubtedly a promising strategy in the near future. It is common practice to compensate participants in trials for specimen collection and transportation. We strongly recommend that a reasonable compensation system that conforms to ethical principles be established for frequent follow-up while ensuring that there is no inducement.

There are also some measures we can take throughout the different stages of a clinical trial. Ensuring that each participant fully gives their consent together with their families, including for the follow-up procedure, is the critical first step. Recording as many contacts as possible, including at least one of the patient's family members, can increase the likelihood of a successful follow-up. During treatment, patient-centred and satisfactory medical care should be provided to build trust with patients and their families, as well as to

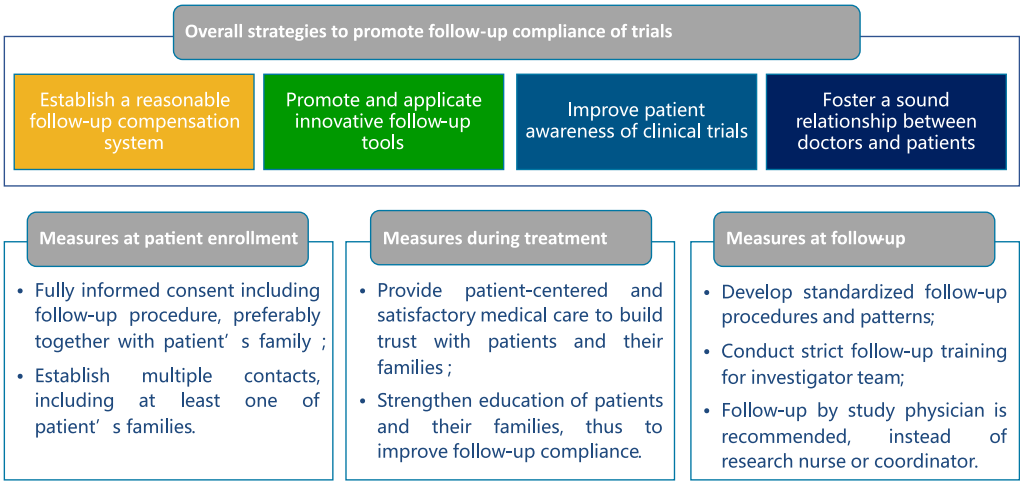

Fig. 1: Overall strategies and detailed measures recommended for promoting follow-up compliance in trials.

strengthen education for them, thus improving follow-up compliance. At regular follow-ups, it is beneficial to develop standardized follow-up procedures and patterns and to conduct strict follow-up training for the investigative team. It is also better to have a study physician, rather than a research nurse or coordinator, who can provide professional medical guidance for patients when necessary.

Conclusion

In summary, this study first raised potentially widespread questions regarding the data integrity and reliability of using OS and other time-to-event endpoints as primary endpoints in drug approval trials due to limited sources of information for the dates of death of participants in clinical trials, which has become even more difficult due to COVID-19. Then, we pioneered the evaluation of 12 potential source scenarios of three methods for obtaining the time of death of participants, including death certificates, death records and follow-up records. With a comprehensive assessment of the 12 scenarios by legitimacy, data reliability, data acquisition efficiency, difficulty of data acquisition, and coverage of participants, both short-term and long-term recommended sources of date of death information and strategies for improving the integrity and reliability of this information were presented. Though all the proposed solutions to the collection of death date could provide reference for all other countries in the world, they are mainly proposed in the context of China.

In the short term, before access to death records and the sharing of EMRs is widely achieved, we suggest that the public security system, an integrated source of death dates, be opened to drug inspection centres appropriately as soon as possible to strengthen supervision. Death certificates provided by participants' family members and detailed standard follow-up records are recommended as two reliable data channels for investigators. In addition, establishing a reasonable follow-up compensation system and standardizing follow-up records with required items, together with three other strategies and six measures at different trial stages, are key elements of a successful follow-up. Meanwhile, we also expect that, under the leadership of the government and the joint efforts of the whole industry, the sharing of electronic medical records and the legal disclosure of death records in established health registries can be realized in the long-term.

Contributors

HYH and YT contributed to framework planning and draft writing, as well as information collection, quality control, analysis and interpretation. NL and GTL led the overall framework planning and data interpretation. YY, AQY, DWW, HF, SHW, CS, XW, QF, YF, QYT, NJ, JTD, HLM, YB, PWM, SMM, DDC, SJX, YLJ, JXZ, QZ, and YL participated in information collection and quality control, LWG, SML, YGS, YYS, ZYL, MHH, SXL, and BHX participated in framework planning, expert opinion, and data interpretation. All the authors reviewed and revised the manuscript.

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Declaration of interests

All authors disclose no competing interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2022.100624.

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