Incidental Imaging Findings in Clinical Trials

Clinical trial end points are outcome measures used to assess the efficacy and safety of an intervention. The selection of end points is based on their perceived clinical importance and accuracy of measurement. If correctly defined and collected, these outcome variables enable the translation of clinical trial data into evidence-based recommendations. Yet as technology changes and clinical practices evolve, emerging clinical events that are unrelated to the study intervention may be missed when conventional end points are used.

In the Scottish Computed Tomography of the Heart (SCOT-HEART) trial, coronary computed tomographic angiography, when added to standard of care, was associated with a 41% lower incidence of death from coronary heart disease or nonfatal myocardial infarction at a median follow-up of 4.8 years. Examination of the incidence of unanticipated radiographic findings and their subsequent diagnostic outcomes was prespecified in the protocol and described in a subsequent report. This approach for clinical trial reporting— including the nature, frequency, and outcomes of incidental imaging findings and new unrelated diagnoses—is the exception to the contemporary norm in reporting the results of trials. However, developing better understanding of the clinical implications of unanticipated imaging findings represents an important opportunity as the use of diagnostic imaging in clinical trials increases.

What is the prevalence of incidental imaging findings? Outside the trial context, their occurrence (referred to as radiographic “incidentalomas”) varies widely, depending on the imaging test, ranging from less than 5% for chest CT for pulmonary embolism to 34% with cardiac MRI. Data about the frequency of incidental imaging findings in clinical trials are limited. It is likely that the magnitude of the phenomenon in clinical research studies is not substantially different from that in clinical practice, although analyses of clinical trial data are needed to answer that definitively.

What are the effects of incidental imaging findings on clinical outcomes of trial participants? Incidental findings are associated with a potential malignancy diagnosis in a sizable proportion of cases. In addition, noncancerous conditions are frequently encountered in the course of an evaluation of incidental imaging findings, including pituitary macroadenomas (30% of pituitary incidentalomas) and cerebral aneurysms (3.9% of brain incidentalomas). Financially, the evaluation of an incidentally detected adrenal nodule, among the most prevalent unanticipated finding, costs $746 to $1745, depending on the investigation modality selected. These unexpected findings and their subsequent evaluation and management have an important bearing on the long-term health of trial participants.

If incidental findings are common and may influence patient outcomes, should they be integrated into trial outcome reporting? It seems that efficacy and safety assessments are incomplete without inclusion of a meticulous synthesis of incidental findings into outcome metrics. Unexpected imaging findings reflect an unintended by-product of the ability of modern technology to scan multiple organs with high-level precision and therefore are a form of safety evaluation. An individual found to have an incidental pulmonary nodule may have to undergo invasive and risky procedures and often submit to long-lasting surveillance imaging (and sometimes active treatment). These interventions therefore may partly counteract the benefit gained with a study intervention. However, incidental imaging findings are a heterogeneous entity. Certain incidentalomas may lead to an objective health benefit with an earlier diagnosis and treatment (eg, nodule representing curable early-stage cancer). Other findings may provide important information about cardiovascular health that could influence future risk-reduction interventions (eg, coronary calcification on chest computed tomography) and thus represent an opportunity to improve cardiopreventive care. In contrast, some incidental findings have no relationship with survival and may pose risks because of invasive evaluation, overdiagnosis, or unnecessary financial expenses.

Investigators have an ethical duty to collect data on and report incidental findings in clinical research, given the important ramifications of such findings on patient health. In addition, researchers have a responsibility to ensure that participants are notified about the possibility of an incidental finding, as part of the informed consent process, as well as to create a mechanism by which information about a finding is disclosed. The latter should occur as soon as a finding is detected to allow timely follow-up and, if needed, treatment. Individuals with certain findings may decide to withdraw from the study, and, although potentially affecting patient retention and outcome data, such a decision should be respected by researchers and the scientific community. Addressing incidental imaging findings in human research by establishing a pathway for communication and discussion with patients has paramount value because it fulfills the principles of patient autonomy and nonmaleficence and embodies respect for participants’ health and well-being—the highest priorities in any clinical trial.

Incorporating incidental imaging findings into trial outcome reporting will require a concerted effort by academia, industry, and regulatory agencies. Defining the scope of the problem will require quantification of the proportion of clinical trials that use imaging tests, including structural and functional modalities. Relevant parameters should include the distribution of patient ages, racial/ethnic groups, and sex in imaging-based clinical trials and the frequency and severity of unanticipated findings in each subgroup. Patient and trial characteristics associated with higher odds of incidental findings should be identified.

In clinical trials that involve imaging studies, investigators and their sponsoring institutions should routinely collect information on unexpected radiographic findings. This includes the index imaging study, the primary organ...
in which the incidental finding was detected, subsequent evaluation (if performed), and anatomic-pathologic diagnosis (if reached). Moreover, imaging-based clinical trials should provide more than just a cross-sectional summary of incidentaloma statistics; they should also collect and track their short- and long-term sequela. This assessment could include clinical, psychological, financial, and societal outcomes.

Methods to categorize incidentalomas into clinical significance groups should be developed. Because incidental findings are a spectrum of disease states ranging from inflammatory or degenerative conditions to overt malignancies, they should be stratified into high significance (conditions likely to affect an individual’s health) vs low significance (conditions unlikely to have an effect on an individual’s health) and when possible be described by a pathologic diagnosis. Such a condition-specific, risk-based classification would standardize incidentaloma outcome reporting and provide insights into the competing health effects of these findings.

Unanticipated imaging findings should not only be characterized but also become de facto clinical trial end points. Measuring and categorizing incidentaloma end points should be conducted in a systematic fashion by designated central end point adjudicating committees. These events should be carefully captured and presented with the standard efficacy and safety end points. Grading systems specific to incidental imaging findings should be formulated and integrated into the Common Terminology Criteria for Adverse Events safety scales. Methods for measuring and reporting incidentaloma findings should be included in trial protocols.

Mandating the reporting of incidental findings in clinical trials is likely to encounter challenges. First, there are various ways in which unanticipated findings are managed in clinical trials. In some cases, the core laboratory reads the imaging studies, identifies the incidental findings, and takes responsibility for the analysis; in other cases, local sites interpret the imaging studies. Laboratories would have to transmit the data to the patient’s primary care physician or other clinician or health care center, who would decide whether to perform further studies. Even if findings are reported to the participant’s primary care physician, it will be difficult to obtain information about what is done with them because follow-up of the incidental finding is sometimes optional and may occur at different sites. Second, reporting and management of incidental findings may vary widely according to geographic region, institutional experience, and physician preference. Thus, in certain cases there may not be a uniform approach to managing abnormal findings. Third, the cost of clinical trials is already very high and mandating incidental finding reporting could increase trial expense and complexity.

Incidental findings are not unique to clinical trials that involve imaging. Investigations in genetics, particularly those using whole-exome sequencing technologies, generate a sizable number of secondary findings, including abnormalities in nontarget genes, as well as molecular variations of unknown relevance.5,6 The debate over investigators’ duties to manage incidental genomic findings has led to the formulation of multiple pathways and consensus statements. One practical approach is based on a 3-way division of secondary genetic findings into those that should be returned (those with high clinical significance and or high reproductive significance), those that may be returned, and those that should not be returned. Incidental imaging findings are different, however, because in most cases a formal diagnosis (and thus the absolute magnitude of clinical importance) cannot be established without additional evaluation, further emphasizing the unique returnability duty for investigators in imaging-based trials.

The optimal evaluation of clinical trial outcomes would be more accurate with an assessment of incidental radiographic findings, as well as incidental genetic findings. The proposed preliminary framework should stimulate discussion among clinical investigators, physicians, regulators, industry, and patient advocacy groups. Incidental findings are often lost data points that matter to both patients and physicians. The time has come to more consistently include them as end points in clinical trials.

ARTICLE INFORMATION

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REFERENCES


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