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Research article

Radiology workflow for RECIST assessment in clinical trials: Can we reconcile time-efficiency and quality?

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ABSTRACT

Purpose: In oncology clinical trials, nonconformity issues are frequently reported. Radiological workload is increasing, thus reducing radiologists' availability and affecting diagnostic quality. We compared performances of a standard radiological workflow (SW) and a novel "hybrid workflow" (HW).

Method: We prospectively studied imaging data of 40 patients included in RECIST 1.1 clinical trials. Ninety-six time-points were reviewed by 7 radiologists and one trained technologist. Nonconformities using the SW were retrieved from hospital archives. For the HW, radiologists performed all baseline evaluations; the technologist made subsequent measurements. Finally, the radiologists checked the technologist's findings before confirming the evaluations. The HW enabled implementation of an electronic reporting system. An independent body compared SW and HW reading times and nonconformity occurrences.

Results: Using SW, 19 types of nonconformity were found: blank report (13%); unsigned report (11%); undocumented change of tumor burden (10%); undocumented new lesions (9%); missing/wrong patients' appointment dates (7%); undocumented tumor location (5%); error in tumor burden change (5%). SW and HW nonconformities affected 55% (179/323) and 5% (2/40) of reports, respectively ($p < 0.001$). HW nonconformities were: one inaccurate login name was used on the platform, and one erroneous time-point number. On average, SW required 11′30″ [10′06″; 13′20″] per time-point. HW required 1′35″ [40″; 5′08″] for radiologists, and 12′18″ [11′12″; 14′18″] for the technologist.

Conclusions: HW significantly reduced the number of trial nonconformities and saved 87% of radiologists' time while enabling them to apply their expertise to final decisions. HW could offer an effective opportunity for cost reduction associated with improved imaging trial quality.

1. Introduction

In 2004, the Food and Drug Administration (FDA) decided to approve drug products according to their effects on surrogate markers, including imaging biomarkers [1]. Since then, imaging modalities and imaging biomarkers have developed considerably, and imaging has become instrumental in assessing drug efficacy and safety. As a result, the proportion of clinical trials involving imaging has increased steadily [2] and on-site radiology departments are faced with a critical additional workload issue, as at our own institution where patients included for trials represent 30% of CT exams.

Although the aim of the FDA was to stimulate drug development by shortening the length and reducing the cost of trials, imaging has now been proved to be a significant cost center [2], adding yet another layer of complexity to data management [3]. The cost and complexity of trials are two items that all the stakeholders are keen to tackle, control and mitigate.

The expected increase in medical imaging in the coming years [4] is coupled with a growing number of diagnosis and response evaluation criteria needing specific expertise [5], training and software assistance [6] to ensure safe and efficient usage. For radiologists, the increased complexity also derives from emerging therapeutics featuring new

Abbreviations: CRA, Clinical Research Assistant; CRF, Case Report From; eCRF, Electronic Case Report Form; FDA, Food and Drug Administration; GCP, Good Clinical Practice; HW, Hybrid Workflow; RECIST, Response Evaluation Criteria in Solid Tumor; SW, Standard Workflow; UFTR, Unstructured Free Text Reporting

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patterns of disease evolution [7] and the multiple imaging modalities involved.

This situation will make data management, analysis and quality control [8] particularly challenging. In addition, the integration of clinical trials into on-site workflow is another major issue.

In practice, the images produced in clinical trials and those made during routine procedures are generally intermingled and feed the same data flow, each adding its constraints to the same workflow. The patients enrolled in trials are scheduled for imaging follow-up appointments and physician consultations as the findings of the imaging follow-up are required for the medical evaluation. The assessments are scheduled and performed on the fly with other routine evaluations.

For radiologists, who generally perform routine activities, involvement in clinical trials increases their workload and raises human resources issues at hospitals which are already running chronic medical deficits [9,10].

In radiology departments managing clinical trials, two kinds of report can be produced per patient.

The oncologic evaluation is mainly documented via unstructured free text reporting (UFTR) in which the radiologist reports on: 1) disease evolution, and 2) any other symptomatic or asymptomatic anomalies. For patients specifically included in clinical trials, the data needed to complete the Case Report Form (CRF) are more specific.

This dual reporting is time-consuming and raises data management challenges that are important to tackle in order to enhance the integration of clinical trials into the routine activity of imaging departments.

Whilst awaiting the benefits of artificial intelligence and fully-automated imaging evaluation, several studies investigated the possibility of extending technologist's role and responsibility [11] [12], but a clear integration of technologist's into a radiology workflow has not been evaluated so far, namely the transfer of all tasks not requiring radiological expertise from the radiologist to the technologist.

In this study, we compared an institutional standard workflow (SW) with a novel cooperative hybrid workflow (HW) for clinical trial follow-ups involving an imaging technologist (under radiologist supervision) assisted by software using electronic-form reporting (eCRF). The comparison focused on reading times and rates of non-conformity occurrence.

2. Material and methods

This study received the agreement of our Institutional Review Board.

2.1. Patients and readers

We prospectively studied imaging data of 40 patients included in a RECIST 1.1 [13] clinical trial (Apr-Dec, 2017) at Centre Antoine Lacassagne, Nice, France. Follow-up was possible for 23 patients; 17 patients underwent baseline evaluation only. Median patient age was 63y, Max = 83y, Min = 37y; 26/40 were male, 14/40 female. Distribution of the diseases in the cohort is presented in Table 1.

Imaging data represented 96 time-points acquired on a CT scanner (GE Optima 64, Japan).

Reviews were performed by 7 senior radiologists with varying levels of expertise (6–10 years' experience) and one technologist (7 years' experience). The technologist underwent specific trainings that included: 1) sessions for advanced use of software dedicated to the monitoring of oncologic patients. Emphasis was placed on the eCRF production; 2) medical sessions; 3) a certification of Good Clinical Practice (GCP) designed for research staff conducting clinical trials with human participants (https://gcp.nidatraining.org/resources). 4) a specific radiologic training on RECIST criteria and their application.

Table 1
Distribution of the diseases in the cohort.

Cancer type	Occurrence	Prevalence (%)
Head &Neck	14	35
Kidney	6	15
Breast	5	12.5
Gastric	4	10
Lung	2	5
Prostate	2	5
Liver	1	2.5
Pancreas	1	2.5
Colon	1	2.5
Testis	1	2.5
Ovary	1	2.5
Esophagus	1	2.5
Parotid	1	2.5

2.2. Workflows

Our study compared two different workflows for the analysis of patient images, including in oncology clinical trials. The two workflows, the standard and hybrid versions, are described below and are illustrated in Fig. 1

a) **Standard workflow**

SW involved radiologists using the Advantage Workstation platform without an electronic reporting system (General Electric, USA).

In the standard workflow, radiologists are the only qualified professionals allowed to perform evaluations. Evaluations included both baseline and subsequent follow-ups.

Image analyses are voice-recorded for documentation of the disease of interest according to RECIST 1.1. Target and non-target lesions are reported and described, as are new lesions. Intercurrent diseases are fully described.

In addition to the voice recording, a RECIST 1.1 formatted paper form (Fig. 2) is manually documented by the radiologist.

b) **Hybrid workflow**

Hybrid workflow involves a computer-aided program, an imaging technician and a radiologist. In a HW setting, radiologists perform all baseline evaluations, which are then saved in the eCRF. The technologist performs the subsequent generic measurements during follow-ups, including checking the registration and measuring target lesions. Also, the technologist seeks and tags new findings as potential new lesions. After each technologist review, a radiologist checks the technologist's measurements and findings. Then, the radiologist confirms the evaluation and triggers the eCRF update. The HW used LMS (XXX, France) featuring an eCRF system, as shown in Fig. 3.

2.3. Study design

In our study, to conform the clinical trial setting, radiologists performed their review using SW. Reading times were recorded and CRF were documented.

In a second step, CRF were forwarded to the technologist to duplicate baseline data on the LMS platform. A radiologist confirmed the correct duplication of measurements. This step was the input for testing the HW.

A third step involved the follow-up of patients in the HW by the technologist, with confirmation by a radiologist. Reading times and eCRF were recorded.

Our study design enabled two different analyses:

a) Comparison of evaluation durations according to the study

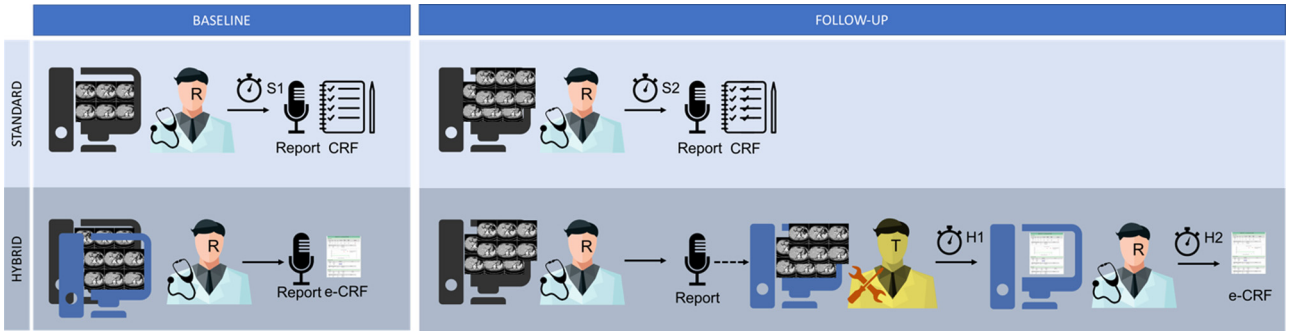

Fig. 1. The Hybrid Workflow. Radiologists performed baseline evaluations. Technologist was in charge of performing subsequent evaluations including measurements of target and also search for new lesions. A radiologist later reviewed and confirmed all the technologist's assessments. For each modification, eCRF was updated with audit trail and finally confirmed by a radiologist.

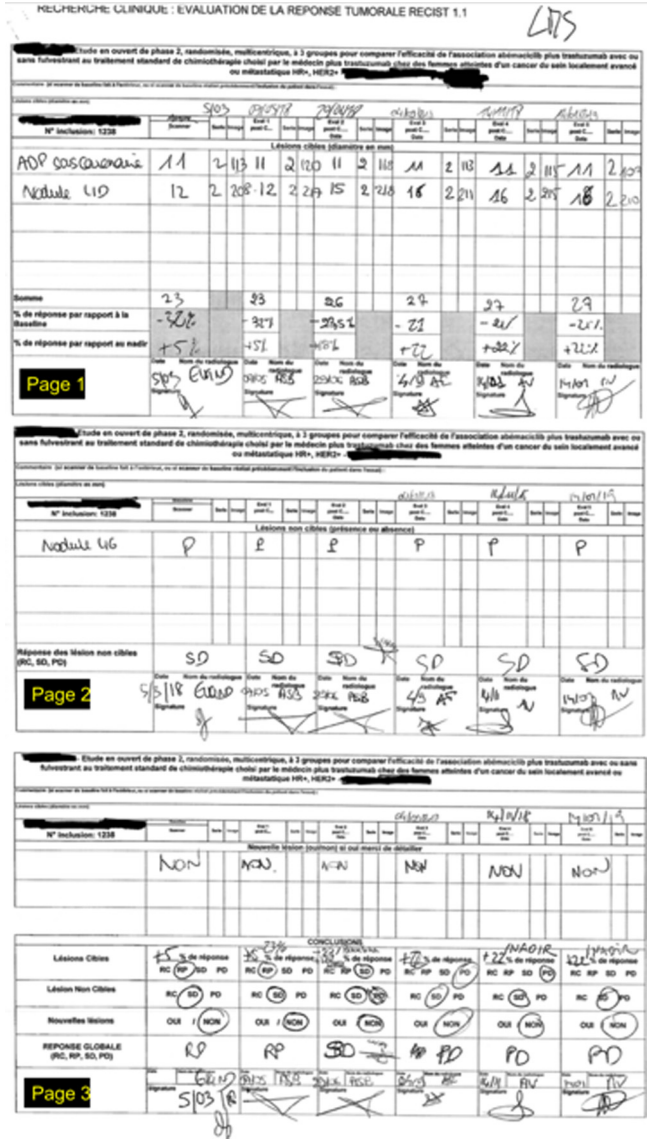

Fig. 2. Display of the RECIST 1.1 paper form reporting. Page 1 for target lesions, Page 2 for non-target lesions and Page 3 for new lesions and global response.

intervention (Fig. 4).

b) Comparison of non-conformities between the two workflows.

This second analysis consisted in checking all eCRF produced by HW (Apr-Dec, 2017). eCRF checks were carried out by an independent third party. Results were compared to the previous year's rate of non-conformities reported in clinical trials involving 207 patients at our institution.

2.4. Metrics

a) **Nonconformities**

As a reference, nonconformities using SW were retrieved from the hospital archives for 2015.

As a test, nonconformities using HW were documented as follows: an independent body reviewed all eCRF produced by the HW and compared the number of nonconformity occurrences against those found in our hospital's 2015 archives. All other HW nonconformities of any kind were also documented.

b) **Reading time** (Fig. 1)

- we measured reading times of radiologists in the SW:

reading times of baselines per patient (S1) and subsequent time-points (S2), assuming that time spent analyzing baseline is longer than for subsequent time-points. We computed average values of S1, S2 and S2/ S1. Knowing S2/S1 makes it possible to infer the impact of workflow improvement for trials with a variable number of examination dates.

- Secondly, we measured the reading time of the technologist in the HW during follow-up (H1).

We also calculated the reading time taken by radiologists in the HW to check and confirm the technologist's measurements (H2)

3. Results

3.1. Analysis of evaluations

At baseline, the total number of reported target lesions was 98 (mean: 2.45 per patient). The distribution of target lesions by disease site is given in Fig. 4a

Also, radiologists reported non-target lesions in 27/40 patients; 59 non-target lesions were reported (mean: 2.2 per patient). The distribution of non-target lesions per disease site is shown in Fig. 4b

The distribution of reported new lesions per disease site is given in Fig. 5. Twenty-nine new lesions were found in 20 patients, predominantly in lungs and bones.

At the last examination, and after the radiologist's confirmation, patients were declared to be: progressive = 5/23, stable = 9/23, or

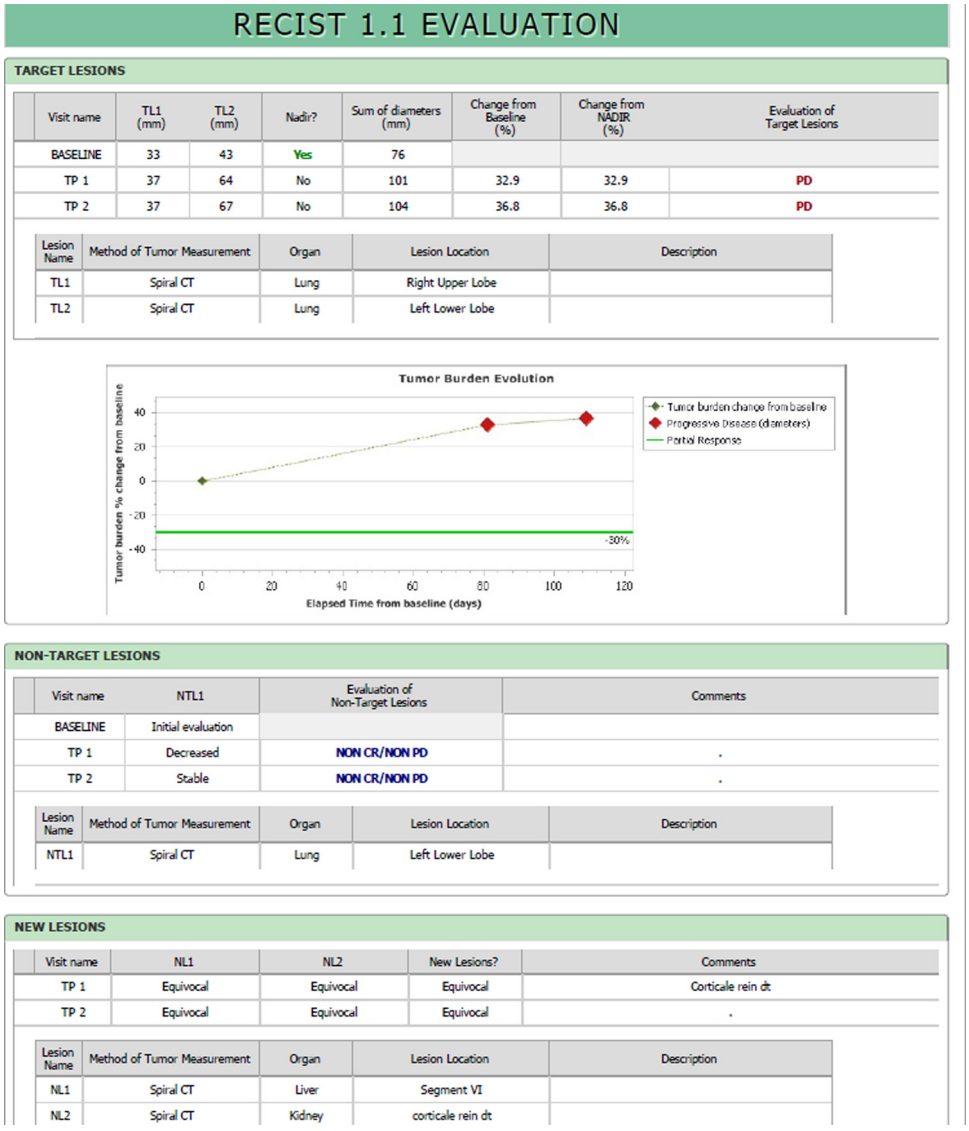

Fig. 3. Display of the response evaluation page of LMS eCRF: LMS eCRF contain all information needed to perform RECIST evaluation along with patient ID and history, reader ID, acquisition and appointment dates. Here, we show a partial view of the RECIST 1.1 evaluation page.

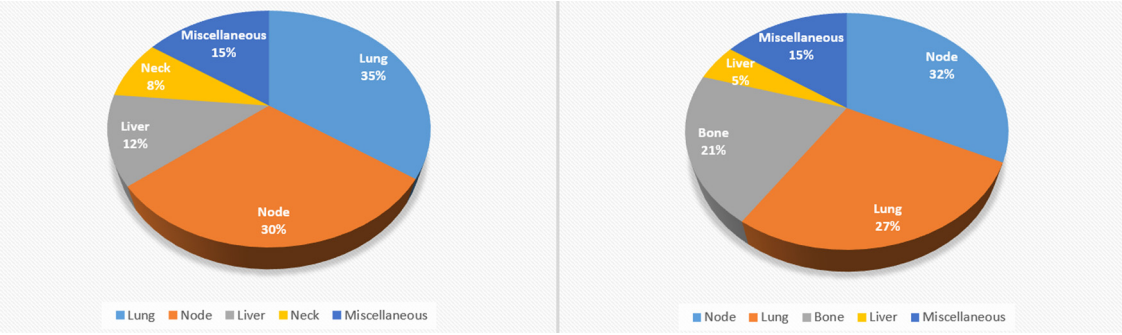

Fig. 4. Distribution of target and non-target lesions. 4a (Left) Distribution of target lesions selected by site of disease during the study. **4b (**Right) Distribution of non-target lesions selected by site of disease during the study.

partial responders = 7/23; 2/23 patients were non-evaluable.

Radiologists had to amend 12/96 eCRF before confirming. In all, 13 modifications were made: 7/13 changes regarding target lesion measurements; 4/13 were missed new lesions (two were peritoneal carcinoses); 2/13 were related to evaluations of non-target lesions.

Interestingly, one new lesion was detected by the technologist that had not been detected by the radiologist. After consensus, the new lesion was taken into account and the patient was classified as progressive.

Following radiologists' revisions, one patient had their status changed. A radiologist changed the status of one non-target lesion from stable to progressive, resulting in a change of patient status from stable

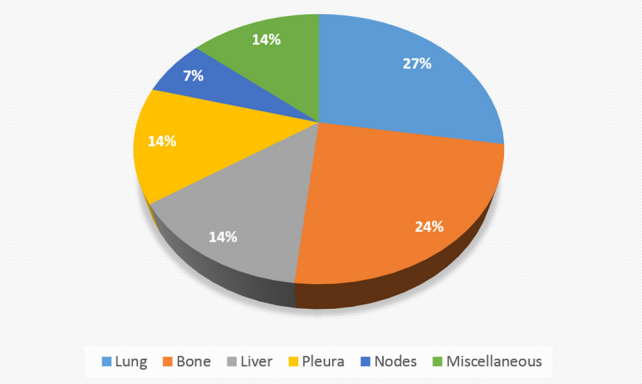

Fig. 5. Distribution of new detected lesions. Distribution of new detected lesions by site of disease during the study.

to progressive disease.

3.2. Nonconformities

Using SW, 22 types of nonconformities were found, as detailed in Table 2.

In the SW, 80 CRF out of 323 (24.7%) were not provided by radiologists.

SW and HW nonconformities affected 55% (179/323) and 5% (2/40) of reports, respectively ($p < 0.001$).

HW nonconformities were: one incorrect login name entered in the LMS platform and one erroneous time-point number.

3.3. Reading time

a) **Baseline vs. follow-up comparison**

Using SW, we recorded non-significant different reading times between baseline and subsequent time- points (P = 0.33).

b) **Comparison between the two workflows at follow-up**

On average, SW took 11′30″ [10′06″; 13′20″] to perform the radiological analysis per follow-up timepoint while HW took 1′35″ [40″; 5′08″] for radiologists, and 12′18″ [11′12″; 14′18″] for the technologist. Box plots of reading times for the different settings are shown in Fig. 6.

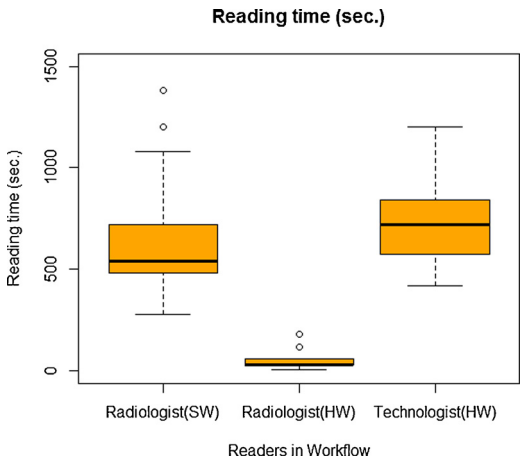

Fig. 6. Distribution of reading time. Box plots of the time required to analyze follow-up images: (Left) for radiologists, in the standard workflow; (Middle) for radiologists to confirm the technologist's assessments in the hybrid workflow; (Right) for the technologist in the hybrid workflow.

4. Discussion

In our study, we found that the involvement of a specialized technologist dedicated to following up evaluations saved nearly 90% of radiologists' time. The modifications made by radiologists before final confirmations concerned fewer than 13% of the technologist's assessments and, ultimately, only 4% of patient statuses in follow-up cases.

In addition, implementation of an electronic reporting system allowed a 10-fold reduction of non-conformities.

Compared with multicenter image interpretations, central reviews may improve data control and readers' performances, thus leading to more robust estimates of treatment effect. However, although central reading is promoted by some institutions [14], central reviews may not always be pertinent [15]. The main trial design features may justify the

Table 2
List of non-conformities.

List of non-conformities	Occurrence	Rate of occurrence
Empty file	22	13%
None of the pages were signed	19	11%
Calculation of % change of the tumoral burden not provided. Not documented	17	10%
New lesion not reported in the file	15	9%
No evaluation at all	13	8%
date of patient visits documented by clinical assistant: Missing date/Wrong Data	11	7%
No slice number (image) documented for lesions No number of the series documented	9	5%
Date of radiologist's signature missing	9	5%
Comments or unusual data written on the file. Non-conformity as it cannot be considered as a source document	9	5%
Radiologist's first name and surname not documented	8	5%
Error in calculating the % of change, response was wrong	8	5%
Sum was not calculated	5	3%
Non RECIST target was selected	4	2%
Switch between target lesion - no impact on tumor burden	4	2%
Document completed in pencil	3	2%
Both target and non-target lesions were not documented	2	1%
Wrong time point was selected as Nadir	2	1%
Erroneous sum. Target lesions were correct but sum was wrong	2	1%
Page where target lesion was documented was not signed	2	1%
Missing CRF or incoherent CRF	2	1%
No target lesion documented	1	1%
Obsolete file version was provided to radiologist	1	1%
TOTAL +	168	100%

use of on-site interpretations provided data-blinding is ensured and bias otherwise controlled.

However, particularly in on-site trials, integration of image interpretation into a hospital's workflow must adapt to the institution's daily routine practice and, primarily, to the available human resources:

- Specific staff trainings are required to ensure consistent response criteria evaluations.
- The additional workload imposed by clinical trials conflicts with the endemic lack of radiologists.
- The additional burden is sometimes distributed between radiologists, thus increasing variability and the risk of human error.

Secondly, the integration must adapt to the hospital's workflow and scheduling:

- Patients are primarily referred for routine appointments. Thus, reports cannot be delayed as in clinical trials. To avoid discrepancies, CRF for clinical trials and UFTR for routine care should be completed simultaneously. This dual reporting complexifies patient tracking and requires close cooperation between research and imaging departments.

Poor integration of clinical trial activity into hospital workflow will result in more non-conformities (in CRF or UFTR) and suboptimal use of radiologist resources.

In everyday practice, there are two methods for documenting CRF:

1) The radiologist oversees both manual completion of the CRF and drafts the UFTR. This workflow is the most time-consuming and, for the above-mentioned reasons, mismatches often occur between CRF and transcriptions from voice recordings [16]. Moreover, one or other or both of these reports can contain mistakes. These quality issues qualify as "non-conformities".
2) To save radiologists' time, a second strategy consists in completing the CRF after, and based on, the UFTR. This task is usually assigned to a Clinical Research Assistant (CRA), who is blinded from imaging data. Finally (generally several days later), the radiologist signs the CRF. In the event of inconsistencies, the radiologist must repeat the procedure thus losing the initial time-saving benefit. Moreover, this data-mining procedure can result in misevaluations in the event of missing data (forgotten by the radiologist), of a misunderstanding of the UFTR, or of transcription errors [16].

With the dual aim of saving radiologists' time and minimizing non-conformities, we designed a workflow managed by a technologist which enables automatic eCRF extraction directly from image annotations.

Based on electronic procedures, HW guarantees reliable data extractions from image measurements with no possible loss of data at this stage. During RECIST evaluations, the technologist follows up the targets selected first by the radiologist at baseline. With this type of workflow, the UFTR provided by the radiologist is the "source" document for the trial. Using this source and the initial baseline, the technologist is charged with producing the eCFR. Any discrepancies between the UFTR and CRF will be detected earlier.

The adoption of HW is not problematic as the radiologists' working environment remains unchanged while the technologist manages the clinical trial software. Indeed, clinical trial software is highly specific and suitable for oncologic evaluations. In contrast, it would be not optimal for reviewing vascular anomalies. As the radiologist needs to inform the physician regarding the entire examination, generic workstations are more useful. In our own design, we used a specialized tool for the quantitative oncologic review. However, when necessary, this kind of tool can also be fully integrated or added, at a click, to the general imaging workstation.

Study limitations:

First, we did not investigate the performance of the hybrid workflow in terms of sensitivity/specificity of therapeutic response. The lack of radiological expertise on the part of the one non-radiologist participant may have biased assessments of the therapeutic response, notably regarding subjective components, such as the assessment of new lesions using RECIST [17]. This possible bias requires further investigation.

Second, only one technologist was involved in the study, therefore limiting the generalizability of our results. In HW, technologist performance is key and, like any image reader, his/her performance is dependent on several factors such as their education, specialized training and the number of images analyzed per week.

A third limitation could be the assumption of equivalence between the two reviewing platforms we used. We adopted the GE platform to compare the time required by a radiologist to assess baseline and follow up images in the SW. We found no significant reading-time differences. For logistic reasons, we did not confirm this equivalence with the HW. A more stringent demonstration would have tested the equivalence of the two platforms in terms of user interface and efficiency of the review.

A fourth limitation concerned a possible Hawthorne effect [18] affecting our results. This bias occurs when a knowingly observed individual behaves differently from one that is not being observed. In our case, the Hawthorne effect could have biased the comparison between non-conformity rate since the non-conformities list (Table 2) was obtained from SW archives whereas non-conformities from HW were derived from observed individuals. However, we believe the Hawthorn effect would have had a limited impact since the vast majority (98%) of non-conformities in Table 2 cannot occur when using a software system [19]. For that reason, our study was more a confirmatory study given that non-conformities listed from SW cannot occur with HW.

Another possible impact of the Hawthorne effect would have been the measurement of reading time. We have no evidence that the absolute values we measured were free of Hawthorne effect. However, we believed that, if any bias has occurred, it would have impacted SW and HW to the same extent, therefore a ratio of 87% saving of radiologist time is an acceptable estimate.

Several groups have analyzed the cost of clinical trials [20], Additional costs cannot be avoided where imaging is involved [2] but these costs can be dramatically reduced by implementing new strategies and technologies. Cost reductions can be made, for instance, by streamlining the complete radiology workflow [21] or by inter-connecting electronic systems [22] with the two-fold aim of reducing manual operations and saving time.

More specifically regarding radiology, it is anticipated that the role of radiologists will evolve towards tasks to which they can bring the highest added value [23]. Given that prospect, HW probably stands halfway along the evolution of radiology workflow, a next step being the enablement of more and more automation and artificial intelligence [24].

These costs can be dramatically reduced by implementing new strategies and technologies that enable physicians to spend less time analyzing images and that reduce the likelihood of errors occurring during image assessment.

HW significantly reduced the number of trial nonconformities and saved 87% of radiologists' time while allowing them to apply their expertise during final decision-making. HW could provide an opportunity for effective cost reduction combined with enhanced quality of clinical trials involving imaging.

Other authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Declaration of Competing Interest

The authors of this manuscript, Hubert Beaumont and Catherine Klifa, declare relationships with the following companies: Median Technologies.

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