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Centers of Excellence

Maintaining high standards of clinical research during the Covid-19 pandemic: insights from an excellence clinical research centre

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Among the many ways the Covid-19 pandemic has harmed society, one is a severe reduction in the global clinical trial activity, ironically concomitant with a tremendous increase in research around the illness, treatments, and vaccines. It has been claimed that around 80% of the non-Covid-19 trials have been stopped or interrupted during the pandemic.[1] This number is supported by data from Clinicaltrials.gov registry, which gave the pandemic as the reason for 86% of the 1052 trial suspensions between March and April 2020.[2]

Medical science is suffering, but so are today's patients who are losing the potential therapeutic benefits offered by clinical trials. In cardiovascular medicine, many trials include vulnerable patients who are at increased risk from severe Covid-19 infection. As a result, plenty of trials have been halted or prematurely ended. It is understandable that patients do not want to participate in elective clinical trials; in fact, patient enrolment appeared to be the main reason for reduced clinical trial activity, due to either a reduction in screening for potential patients or logistical difficulties with treatment delivery.

At the same time, scientific authorities and research centres have done their best to protect the already enrolled participants. The European Medicines Agency and United States Food and Drug Administration issued guidance on strategies to deal with the consequences of Covid-19 and to adapt patients' care to the new context, calling for urgent amendments of protocols.[3,4]

The dismal situation is not unavoidable, however. There are a number of examples of successfully conducted cardiovascular research since the pandemic started. As researchers we have an opportunity to learn from how other institutes have coped with the pandemic. We here describe our experience from the National University of Ireland (NUIG) and Galway University Hospital before and during the Covid-19 pandemic. Local situations differ, but some of our learnings may be of use to other cardiovascular hospitals and research centres.

We conducted a retrospective analysis of our local databases, reporting data for patient screening visits, clinical trial enrolment rates, and follow-up visits of ongoing trials in the field of interventional cardiology at NUIG. Data are available under formal and reasoned request to the corresponding author. The analysis included a period of 2 years, from March 2019 to April 2021. Two groups were defined according to the presence of Covid-19 pandemic: pre-pandemic (March 2019–February 2020) and pandemic (March 2020–May 2021) periods.

Overall, 23 different clinical trials were ongoing during the study period. Twelve were active during the pre-pandemic period; 3 of these completed as planned before March 2020, while 9 continued. With 11 trials initiating during the pandemic, 20 trials were ongoing between March 2020 and May 2021.

Trials were grouped according to the investigated topic: coronary procedures, structural interventions, heart failure endovascular treatment, hypertension endovascular treatment, and other endovascular procedures. During the pre-pandemic period, three trials involved coronary procedures (25%), one trial concerned endovascular devices for heart failure (8.3%), one regarded endovascular treatment of hypertension (8.3%), no studies included structural interventions (0%), and seven were related to other endovascular interventions (58.3%).

During the pandemic period seven trials involved coronary procedures (35%), four endovascular hypertension treatment (0%), two device implantation for heart failure patients (10%), one structural interventions (5%), and six other endovascular interventions (30%).

The total number of screening visits, enrolments, and follow-up visits amounted to 1078 over the 2 years. Of these, 360 were carried out before the pandemic, while 718 during the pandemic period, with a significant increase of 33.2% ($P = 0.019$).

Compared to the pre-pandemic year, during the pandemic year, we significantly increased the proportion of visits and enrolments for coronary trials (52 vs. 198; 14.5% vs. 27.6%, $P = 0.032$) and structural trials

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(0 vs. 103; 0% vs. 14.3%, $P < 0.001$). Heart failure studies visits and enrolment rates resulted comparable between the two periods (24 vs. 82; 6.6% vs. 11.4%, $P = 0.370$).

In contrast, the proportion of visits and enrolments for trials about hypertension and other endovascular treatments decreased during the pandemic: 200 vs. 273 (55.5% vs. 38.1%, $P = 0.010$) and 84 vs. 62 (23.3% vs. 8.6%, $P = 0.013$), respectively. Trends in absolute and relative numbers are depicted in *Figure 1*.

As these numbers show, NUIG not only maintained but even increased our clinical trial activity during the Covid-19 pandemic. There are probably multiple reasons for this (*Figure 2*).

Dedicated involvement of senior investigators is crucial to the success of clinical research programmes in general and in the challenging environment of a pandemic in particular. A group of expert interventional cardiologists with significant experience in clinical research, supported by the Higher Education Authorities and Science Foundation Ireland are involved in the development, initiation, and conduct of all trials at NUIG. Weekly meetings are held to sort out any issue related to research studies, to avoid delays and ensure consistent decisions and directives.

Second, a dedicated *research team* seems to have helped. The presence of a working group composed of senior research nurses and clinical fellows dedicated to research supports the maintenance of organizational standards and a clear distribution of tasks. Every team member has a defined role, interacting with other members' roles, but tailored to individual skillsets and preferences.

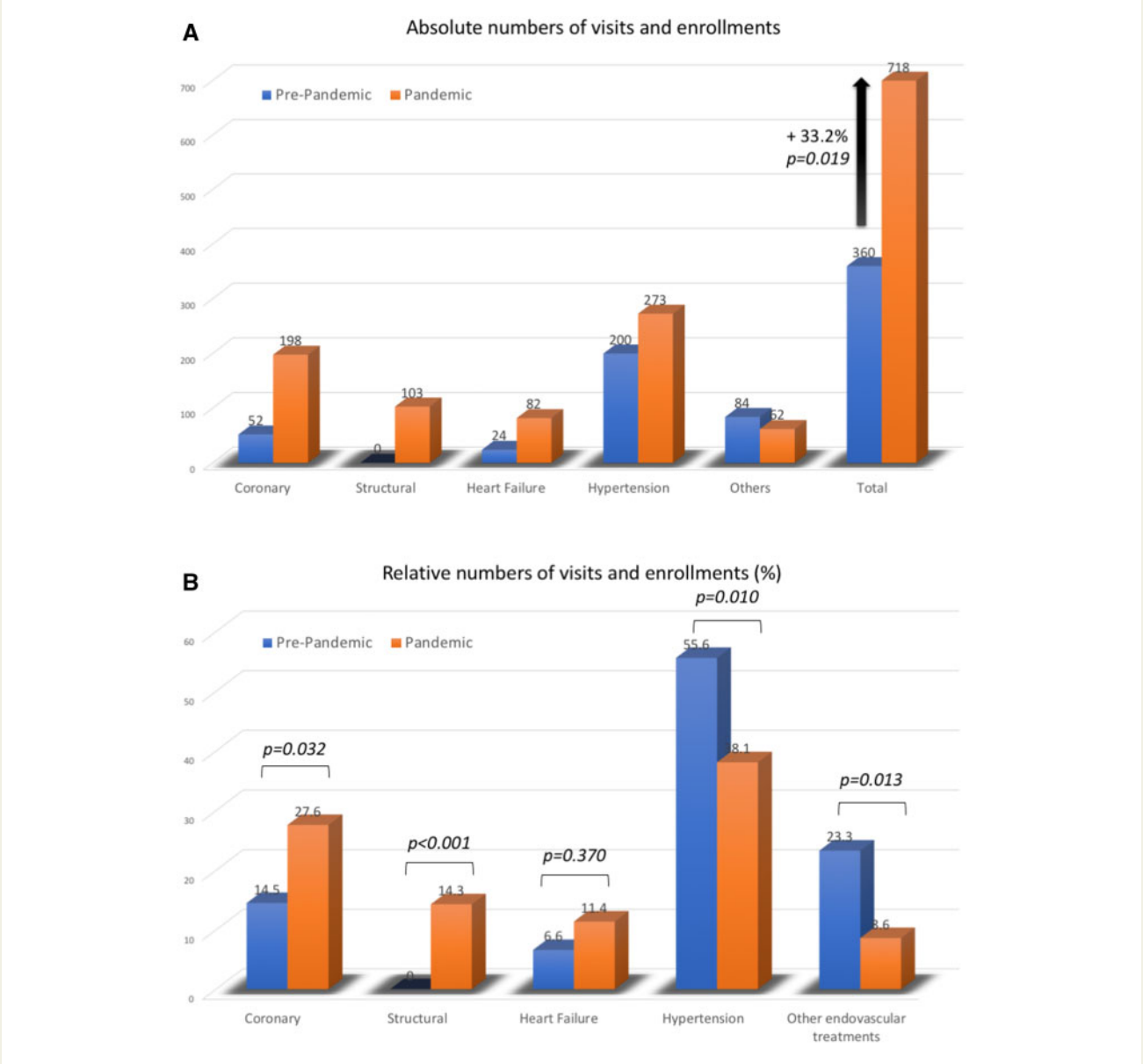

Figure 1 (*A*) Absolute numbers trends of screening, enrolment and follow-up visits during the pre-pandemic and pandemic period, at the University Galway Hospital. (*B*) Proportions changes of trials visits and enrolments according to the study types during the pandemic, at the University Galway Hospital.

Figure 2 Reasons leading to clinical research activity success during Covid-19 pandemic.

Third, focusing on *life-saving clinical studies* brings benefits to participating patients and study withdrawal might be life threatening. All studies in our analysis addressed real needs and most represented life-saving treatments for patients with cardiovascular conditions. Indeed, our data showed an increased proportion of trials related to coronary and structural interventions during the pandemic. This favoured the continuation of screening, enrolment and follow-up visits despite pandemic-related obstacles.

Fourth, recruitment from *private health facilities*. The private hospitals in the area were Covid-19 free. This allowed high risk patients to be screened for Covid-19 and if negative, to be offered elective clinical trial procedures in the facilities. Additional ethics and clinical trials contracts were signed with the private hospitals to allow continuation of clinical trial service.

Fifth: *virtual proctoring*. Initiation visits and practical proctoring for operators are fundamental at study initiation, in particular in the interventional medicine field. During the Covid-19 pandemic NUIG has introduced remote training for all staff, with simultaneous proctoring during interventions in order to continue ongoing studies and permit new trials to start. We implemented secure and high speed internet in the cath-labs, and placed two additional computers in the control room and in the labs, for the proctors to observe and advice operators during procedures.

Sixth: *telemedicine*. This is the most common strategy implemented worldwide to keep high standards of care for the patients. When possible, all on-site visits were converted to virtual meetings, allowing timely follow-up consultations.

Seventh: *safety measures*. To ensure the availability of in-person encounters, preventive measures were applied, with dedicated spaces assigned to research purposes, avoiding close contacts. Every person who enters the research centre is screened for Covid-19 symptoms, fever and potential exposure. Masks and physical distancing were required for all in-person interactions and no visitors allowed, except for one carer in the case of patients with disabilities.

Conclusions

A combination of pre-existing and adaptive factors allowed clinical research at NUIG to respond to the multiple challenges posed by the Covid-19 pandemic. There was an inclusive clinical research platform for clinical investigations in interventional medicine; a solid pre-existing organization, highly motivated workforce, public/private collaboration, and not least, the fact that cardiovascular studies often involve life-saving therapies.

Continued success is not guaranteed, however. The pandemic is not past and Covid-19 may affect key study outcomes. Multiple reports around the world confirmed a large Covid-19-related reduction in ACS admissions, with an adverse effect on patients' outcomes due to delayed treatment or missed presentation. Covid-19 infection could raise or lower blood pressure in patients with hypertension leading to

over- or underestimations of adverse events captured in clinical endpoints. Participants are also likely to have changed their lifestyle, adding a confounder. Researchers should be aware of these considerations in the future analysis and interpretation of trials results.[5]

Bearing in mind all these limitations, future clinical research should also take advantage of the new strategies implemented during this particular period, in order to improve and accelerate the scientific progress.

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Global spotlights

Retractions in medicine: the tip of the iceberg

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In 1983, in the aftermath of what was then considered one of the most significant cases of scientific fraud ever, *The New York Times* reported that 82 papers by John Darsee, formerly of Harvard and Emory, had been retracted (available at https://www.nytimes.com/1983/06/14/science/notorious-darsee-case-shakes-assumptions-about-science.html). That idea persisted: ∼30 years later, *Nature* said that >80 of Darsee's papers had been withdrawn.[1]

In truth, just 17 papers by Darsee have ever been retracted (available at: http://retractiondatabase.org/RetractionSearch.aspx#?auth%3dDarsee%252c%2bJohn%2bR). That may seem surprising, given how high-profile the case was, but we have learned in the decades since that thousands—or even tens of thousands—of papers that should have been retracted have not been.

Last year, there were >2300 retractions, up from just 38 in the year 2000 (*Figure 1*).[2] Even accounting for the growth in papers published, the rate has increased dramatically. There are far more eyeballs on papers today, including the eyeballs of sleuths who find image manipulation, plagiarism, duplication suggestive of paper mills, statistical anomalies, and other issues (available at: https://retractionwatch.com/2018/06/17/meet-the-scientific-sleuths-ten-whove-had-an-impact-on-the-scientific-literature/).
Take the example of John Carlisle, an anaesthetist whose work spotting data too good to be true, and randomization issues, has led to scores of retractions, including one in the *New England Journal of Medicine* (available at: https://www.npr.org/sections/health-shots/2018/06/13/619619302/errors-trigger-retraction-of-study-on-mediterranean-diets-heart-benefits).

Still, retractions remain a relatively infrequent occurrence, on the order of four in 10 000—0.04%—published papers.[3] While the rate may appear to be plateauing or even declining in some fields,[4] the amount of time that retractions typically take means that the data lag.

Regardless of the true rate, however, it is clear that far more papers should be retracted than are being retracted. We can say this with confidence because of several factors. First, it is not unusual for journals—as in the Darsee case—to fail to retract papers despite official requests for retraction from universities or government agencies following findings of misconduct.[5] Second, sleuths with good track records for accuracy routinely complain—with good reason—that only a fraction of the papers they flag to journals are ever acted on (available at: https://www.the-scientist.com/news-opinion/eye-for-manipulation–a-profile-of-elisabeth-bik-65839).

While it is impossible to know with certainty just how much of the literature is flawed enough to be retracted, we may derive some clues. A 2009 systematic review and meta-analysis of surveys found that 2% of researchers admitted to committing misconduct[6] and a 2016 study found that a very similar percentage of a large sample of papers included evidence of deliberate image manipulation.[7] Two percent is, of course, much larger than 0.04%.

What explains this discrepancy? Here, too, we can point to a number of factors (see *Table 1*). One is the 'publish or perish' system that rewards publication in journals nearly exclusively and leads to fierce pushback on any criticisms of papers, particularly critiques that could lead to retraction. Another is lawyers hired by authors, who as *Nature* has acknowledged can slow down the process or grind it to a halt.[8] And content management systems used by publishers still struggle with retraction processes.

Times are, however, changing. It has become more difficult for authors, institutions, and journals to ignore critiques on sites such as PubPeer.com. Some journals are hiring research integrity managers whose role is to

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