
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

reported in other studies.[2,3] Other endpoints, such as complication rates, mortality, resection margin status, and number of retrieved lymph nodes, did not differ between the two groups. These findings mean that the present trial by the MITG-P-CPAM is a very well performed but nonetheless negative study. In this regard, it is consistent with data from previous randomised controlled trials on the topic,[2–4] and with a recent meta-analysis of these trials,[5] that collectively document similar perioperative outcomes after LPD and OPD, concluding that there are no advantages of the laparoscopic technique over the open technique.

Third, achieving the supposed benefit of 15 versus 16 days in terms of length of stay—according to previous work by the MITG-P-CPAM[6]—necessitates a learning curve of 104 LPD procedures done by the individual surgeon. Advanced techniques in pancreatoduodenectomy for cancer, such as level-one dissection alongside the superior mesenteric artery,[7] arterial divestment,[8] or arterial resection,[9] will bring about even more extensive learning curves. The conclusion is that the individual surgeon would need to do more than 100 LPD procedures to obtain outcomes similar to the OPD procedure. Compare this number with an annual caseload of 20–75 pancreatic head resections in mid-volume and high-volume surgical centres and you get an idea as to the practicability and benefit of the approach. Importantly, when performed in centres with an annual caseload of 20 or more pancreatoduodenectomies, LPD has been associated with a disturbing increase in fatalities due to procedural complications, which led to the premature termination of the LEOPARD-2 trial by the Dutch Pancreatic Cancer Group.[3]

The recent Miami International Evidence-based Guidelines on Minimally Invasive Pancreas Resection rightly conclude that there are insufficient data to recommend LPD over OPD.[10] The present study by the MITG-P-CPAM group contributes an important piece to the puzzle of whether LPD for pancreatic cancer, albeit feasible at high-volume centres, is an innovation that hospital organisations and health-care systems should invest in. The most probable answer is that the marginal benefits of LPD do not warrant the obstacles of an extensive learning curve,[6] safety concerns,[3] and economic and infrastructure hurdles associated with the procedure. Such an answer would confirm a basic principle in surgery: success does not depend on technical feasibility but on adapting technical advances to true medical needs and, most importantly, to the benefit of the individual patient.

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# Affordable treatment and political commitment are crucial to eliminate hepatitis C globally

It has been nearly 10 years since highly effective, all-oral, direct-acting antiviral (DAA) treatments triggered a revolution in hepatitis C care and treatment. DAAs led to optimism that hepatitis C could be eliminated, and in 2016 WHO set targets to eliminate hepatitis C as a public health threat by 2030. Specifically, WHO called

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for an 80% reduction in new chronic infections and a 65% reduction in mortality from that reported in 2015.[1] However, many countries are likely to miss these targets,[2] with the COVID-19 pandemic worsening matters.

Many countries' hepatitis C elimination efforts are lagging because of the cost of DAAs. Although their price has reduced markedly since they first came onto the market (approximately US$1000 per pill) in 2014, treatment remains unaffordable for many people. In high-income countries with strong public health systems or comprehensive insurance programmes, the price of treatment has been negotiated to a cost that enables the population to access care; however, in many other high-income countries, treatment remains unaffordable, presenting a major barrier to scale-up.[3] In low-income and middle-income countries (LMICs), voluntary licensing and the Medicine Patent Pool has enabled access to DAAs at less than $60 per treatment course, and, in certain countries, patents for some DAAs have allowed generic manufacturers to set up local production without a license.[3] However, as highlighted by Isabelle Andrieux-Meyer and colleagues[4] in *The Lancet Gastroenterology & Hepatology*, nearly 50 middle-income countries, estimated to have 43% of the global hepatitis C burden, have been excluded from the license agreements of originator companies for key DAAs, making treatment unaffordable for most of their citizens.

In an effort to address this crucial issue of treatment affordability, Andrieux-Meyer and colleagues[4] studied the efficacy and safety of ravidasvir plus sofosbuvir in people with chronic hepatitis C. Ravidasvir is a non-structural protein 5A inhibitor supported by the Drugs for Neglected Diseases *initiative* in the hope of providing an affordable pangenotypic regimen when used in combination with sofosbuvir. STORM-C-1 is the first part of an open-label, single-arm clinical trial with 301 participants in Malaysia and Thailand (98 [33%] with genotype 1a, 27 [9%] with genotype 1b, two [1%] with genotype 2, 158 [52%] with genotype 3, and 16 [5%] with genotype 6), of whom 81 (27%) had compensated cirrhosis, 90 (30%) had HIV co-infection, and 99 (33%) had previous interferon-based treatment. Key findings in this interim analysis were an overall sustained virological response at 12 weeks after treatment (SVR12) of 97%, an SVR12 of 97% in participants with genotype 3 (a subgroup of patients who have lower SVR12 with some regimens), and an SVR of 96% for participants with cirrhosis. SVR12 rates were unaffected by HIV co-infection or previous interferon treatment history.[4]

The outcomes of STORM-C-1 are encouraging. ravidasvir appears to be an affordable option that could help reduce treatment costs, particularly in middle-income countries that are stuck in the middle—ineligible for the licensed generic drugs but unable to afford current pangenotypic regimens.[5] However, STORM-C-1 had some limitations. It excluded participants who reported current injecting drug use and hepatitis B co-infection; additionally, SVR12 was lower in those with genotype 6, and no participants had genotype 4. Of note, in a previous study from Egypt examining the efficacy of ravidasvir and sofosbuvir with or without ribavirin, participants with genotype 4 HCV infection had high SVR12 rates.[6]

Although the cost of DAA treatment is important, achieving the WHO 2030 elimination targets requires more than affordable treatment. The availability and affordability of diagnostics remains a major barrier to treatment scale-up, particularly in LMICs. In 2020, prices were $1–8 per test for WHO-prequalified HCV antibody rapid diagnostic tests, but many countries cannot purchase rapid diagnostic tests so cheaply.[3] Moreover, many health systems require restructuring to meet the needs of individuals who require care; this includes moving care into community settings, supporting task-shifting to reduce reliance on doctors and other highly qualified but few in number medical personnel, and reducing numbers of clinic visits through simplified testing, including point-of-care testing.[7]

Finite resources mean countries must make difficult choices as they work to achieve universal health coverage, a target for 2030 in the UN Sustainable Development Goals.[8] Countries are advised to identify which interventions to prioritise in their national health benefits package. In making decisions about the composition of health benefits packages, WHO recommends prioritising interventions using three criteria: cost-effectiveness, priority to the worst off, and financial risk protection.[9] Lowering the cost of treatment through the availability of drugs, such as ravidasvir, is important to improve cost-effectiveness.

However, it also requires political commitment to negotiate and address regulatory and intellectual property barriers. An example of such an approach is in Malaysia, where there has been strong political commitment to support public health programmes and to make HCV treatment available and affordable for the population. Pharco (Alexandria, Egypt) has committed to making the ravidasvir and sofosbuvir combination, once approved, available at a price of $300 or less per treatment course,[10] representing a hundredth the cost of the existing originator DAA regimen.

Countries also need high-quality surveillance data to identify which health interventions to prioritise and include in their health benefits package. Absent in many countries, high-quality data about hepatitis C is crucial to enable countries to measure and understand the financial risk associated with the direct and indirect costs of hepatitis C morbidity and mortality. Doing nothing has real but often unrecognised costs. The paucity of data, combined with concern about costs, could prevent many countries from meeting the 2030 hepatitis C elimination targets, despite the demonstrable economic benefits of doing so.[9]

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# Optimising clinical trial design to manage placebo response in randomised controlled trials of irritable bowel syndrome


Ikon Images/John Holcroft/Science Photo Library

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Irritable bowel syndrome (IBS) is the most common gastroenterology referral and is defined by abdominal pain associated with altered bowel habits. In the absence of objective biomarkers, patient perception of symptoms means everything. Evaluating IBS treatment response in practice relies on the physician to ask their patient if they feel better. A simple question, yet one that is greatly influenced by preconceived expectations of treatment outcomes, frequency of care received, and even side-effects of treatment, which can predispose a patient toward perceiving that a treatment is working.[1–3] As recently as 10 years ago, the basic question of whether a patient achieved adequate or global relief of symptoms was the most common (and most sensible) endpoint for clinical trials. Yet this endpoint yielded placebo response rates reaching around 40%. Taken even further, active placebo (with informed consent) has even shown promise as an IBS treatment.[4] These realities allude to the challenges in evaluating investigational IBS treatments in randomised, placebo-controlled trials.

The high placebo response associated with straightforward clinical response questions poses at least two barriers to innovation in IBS care. First, as in other diseases such as asthma, physiological treatment responses might be obscured by high, non-specific