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Conducting randomised controlled trials across countries with disparate levels of socio-economic development: The experience of the Asia-Pacific Hepatocellular Carcinoma Trials Group ☆

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ABSTRACT

Hepatocellular carcinoma (HCC), which constitutes over 85–90% of all primary liver cancers, is the most predominant type of liver cancer, and the third leading cause of cancer related deaths in the world. While the Asia-Pacific is a highly heterogeneous region in geography, ethnicity and in the level of socio-economic development, the main burden of HCC falls in this region and there are compelling reasons and advantages to conduct definitive clinical trials in HCC where it is endemic. The Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group was established in 1997 and has faced and overcome challenges that are inherent in conducting clinical trials in a disparate region. Clinical trial infrastructure is rudimentary at many sites and requires significant effort to be expended on training and monitoring to ensure production of definitive data. The benefits of industrial support of Investigator-Initiated Trials are discussed in the context of the Asia-Pacific. The positive experience of the AHCC trials group would be valuable to any collaborative trials in countries with disparate levels of socio-economic development.

1. Introduction

Hepatocellular carcinoma (HCC), which constitutes over 85–90% of all primary liver cancers, is the most predominant type of liver cancer, and the third leading cause of cancer related deaths in the world [1]. It has been estimated that HCC results in 650,000 deaths yearly, of which two-thirds are from Asia [2].

While HCC itself has been reported to be associated with many risk factors including dietary aflatoxin exposure [3], alcohol consumption [4], obesity [5] and diabetes [6], chronic viral hepatitis is most important risk factor [7]. The geographical prevalence of HCC in this region is attributed to the high incidences of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, the main etiological agents for HCC [8–11]. HBV and HCV account for 80–90% of all HCC worldwide [12].

The resources and expertise required to conduct randomised controlled trials (RCT) were previously confined to economically more developed nations, mainly outside of the Asia-Pacific. There was a consequential paucity of randomised controlled trials in HCC in the endemic regions of the Asia-Pacific and other developing nations.

Clinicians in Asia however share a common goal of seeking efficacious treatment for a cancer epidemic in the region that

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had few available therapeutic options. This impetus marked the beginning of the AHCC trials group. Subsequently other groups in the region similarly embarked on multi-centre cancer trials namely the Aspirin for Dukes C and High Risk Dukes B Colorectal Cancers (ASCOLT) trial [13] and the Nimotuzumab and Cisplatin/Radiotherapy for locally Advanced Head and Neck Squamous Cell Cancer trial [14].

2. History of the trials group

The Asia Pacific Hepatocellular (AHCC) Trials Group was created in 1997 when its first randomised controlled trial in hepatocellular carcinoma (HCC) was initiated by the Singapore General Hospital, and the NMRC Clinical Trials and Epidemiology Research Unit (CTERU), Singapore [15]. This started as a single centre prospective HCC clinical trial at the Singapore General Hospital. Within a year this expanded to a multi-centre trial in the Asia-Pacific region when centres from leading universities and hospitals from Hong Kong, Bali, Malaysia, Myanmar, Thailand, Australia, Korea and New Zealand joined the trial. The enterprise evolved into the first collaborative oncology trials group in the region. Collectively the group believes that definitive clinical trials on HCC should be carried out where the disease is endemic, and that they should benefit patients who would otherwise not have access to cutting-edge therapies. The main objectives of the group are to conduct preventive and therapeutic trials in HCC, to carry out basic and translational research in this field, and to develop training and educational programs in HCC [16]. After 15 years of conducting multi-centre, multi-national clinical trials, the AHCC network has morphed into a well-established platform for high-quality clinical studies. More than 30 centres from 14 countries have taken part in clinical trials of the AHCC trials group (Table 1). The group has launched 6 multi-centre HCC clinical trials, the latest being the AHCC 06 (SIRveNIB) trial which commenced in 2010 (Table 2).

3. Paradigm shift: conducting clinical trials in the developing nations of Asia-Pacific

The AHCC trials group was formed at a time when there was very little interest from the pharmaceutical industry to conduct or support randomised controlled trials in the Asia-Pacific in HCC or other diseases [17,18]. This has changed in the last decade. This paradigm shift was fuelled by mainly economic factors including the rapid expansion of the pharmaceutical industry, the significant potential of new markets, and cost-effectiveness mostly due to relatively cheaper costs of conducting clinical trials in the region. In addition, there has been improving quality of medical infrastructure, and considerably reduced amount of regulatory barriers required for drug approval in the region [17,19].

However while the advantages of conducting clinical trials in Asia are economically apparent, there are also social and scientific imperatives. The Asia Pacific is a highly diverse geographical region comprising of countries with vastly disparate levels of socio-economic development [20,21] and different ethnic populations. A commonly overlooked but relevant advantage of conducting RCTs in Asia-Pacific is that the heterogeneity of this region reflects the clinical reality of the disease on the ground. The large number of potential research participants in this region permits ample opportunities for RCTs to achieve definitive outcomes because of the high disease incidence rates and availability of epidemiological data from a highly representative population.

Well-conducted clinical trials based on sound scientific premises offer opportunities for patients to have access to promising new therapies. Conducting RCTs in the Asia-Pacific thus directly benefit patients in many developing countries who otherwise would have no access to new therapies, and this potentially brings about better patient outcomes in economically disadvantaged nations.

HCC trials in this region also provide opportunities to characterise this disease through the elucidation of prognostic biomarkers, and the varied genetic and environmental influences that affect pathology and treatment responses across different ethnicity and populations.

Clinical trials in such a diverse region are however also accompanied by significant challenges.

4. Meeting the challenges

From the inception of the first AHCC Trial in 1997, the trials group faced novel and significant logistical challenges. These challenges remain similar today, and the lessons learnt are widely applicable.

There were evident gaps in experience with local or multinational trials in some of the member sites of the AHCC trials group. Many centres were from countries that were challenged in socio-economic development and hence also largely rudimentary in medical facilities, infrastructure, and even indemnity assurance. At the other end of the spectrum, countries in the region that are ranked top globally for Gross Domestic Product (GDP) per capita, including Singapore, Korea, and New Zealand [21] were better prepared for clinical trials.

When the first multi-centre trial was launched, there was general anxiety on the feasibility of conducting good GCP-standard clinical trials although there were also compelling pluses that performing RCTs in the Asia-Pacific would bring. Ensuring that Good Clinical Practise Guidelines (GCP) were in place was of paramount importance. Differences in the standard of care and cultural practices could also potentially affect implementation of the study protocol [22]. The heterogeneity of different sites required site management that was tailored to the economic status, culture, religion, language, medical infrastructure, and amount of RCT experience that each country possessed.

The AHCC trials were successfully conducted with strict adherence to GCP guidelines, through repeated informative audits and frequent inspections and monitoring of trial sites. For example, 100% audit for the AHCC02 trial was adopted and such audits were highly educative for site personnel.

Sites which were new to such guidelines required significant investment in staff training to efficiently conduct the trials in a GCP-compliant manner. An example would be a significant amount of time spent in training inexperienced but enormously valuable sites in Mongolia and Bali on fundamental trial procedures, e.g. setting up Institutional Review Board (IRB)s, reporting of adverse-events etc. Some of these sites require the approval of multiple institutional boards.

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