	REGULATION 28 REPORT TO PREVENT FUTURE DEATHS THIS REPORT IS BEING SENT TO: [redacted] Head of Enforcement, MHRA Medicines and Healthcare Products Regulatory Agency, 151 Buckingham Palace Road, London SW1W 9SZ
1	CORONER I am Andrew Harris, Senior Coroner, London Inner South jurisdiction
2	CORONER'S LEGAL POWERS I make this report under paragraph 7, Schedule 5, Coroners and Justice Act 2009 and regulations 28 and 29 of the Coroners (Investigations) Regulations 2013.
3	INQUEST On 23rd August 2015, I opened an inquest into the death of **Mr Maurice Macdonnell who died on 16.08.16 in Kings College Hospital;** [redacted] It was concluded on 24th May 2017. The medical cause of death was: 1a Giant cell and lymphohistiocytic myocarditis and myositis 1b Rare immune related adverse reaction of an immune checkpoint inhibitor in a clinical trail for treatment of hepatocellular carcinoma. The conclusion as to the death was: Unintended consequence of consented pharmaceutical treatment in a drug trial for advanced cancer..
4	CIRCUMSTANCES OF THE DEATH Mr Macdonnell was diagnosed with advanced liver cancer in May 2016 and chose to participate in an international randomized clinical trial (Study CA209-040) of Nivolumab v the standard relatively ineffective treatment with Sorafenib. 10 days after the first dose of the trial drug, he developed a ptosis and became progressively fatigued. At review at 14/7 on 8th August he was administered a second dose of the drug before a diagnosis of the cause of the ptosis had been made. This was not a breach of trial protocol (although 2/7 later the pharmaceutical company advised withholding the drug) and there is insufficient evidence to conclude that the decision contributed to the death. He did not report muscle pain or breathlessness. Clinical examination, blood tests and CT scan excluded non drug causes of ptosis and he went home. Neurological advice suggested an urgent MRI scan was done. However he became progressively weaker at home, his GP attending on 15th. He became unsteady and incontinent in the night and arrested on the way to King's College Hospital the next morning, due to progressive myositis and myocarditis, without further investigation.

5	CORONER'S CONCERNS During the course of the inquest, the evidence revealed a matter giving rise to concern that in my opinion means that there is still a risk that future deaths will occur unless action is taken. In the circumstances it is my statutory duty to report to you. The MATTER OF CONCERN is as follows. – The decision to administer the second dose after fatigue and ptosis had developed was taken by the doctor who was also the investigator in the research study. There would appear to be a conflict of interest between the benefits of keeping the patient in the trial in the interests of research and the potential risks to health of the patient from receiving the second dose, if that decision is taken by the same doctor. [redacted] Director BMS R&D advised that the research had received UK Ethics Committee Approval, but this approval was not received as evidence by the court. He advised in his experience in international drug trials, there was no such arrangement of different doctors to deal with this conflict of interest. He pointed out that the severity of reaction was not enough to require stopping the drug, according to the protocol, but he would want the drug stopped if it was likely the changes were related to drug administration. He encouraged clinical exploration of alternative diagnoses. The letter of response to the enquiry made of BMS by the research nurse advised "hold any further study drug administration". After the inquest the R&D director wrote to the coroner explained the extensive training of investigators and they have access to a medical monitor, who attends a committee to see if any modifications are required in the trial for safety reasons. He also informs the court that introducing an independent adjudicator could pose a risk of bias and a burden of bureaucracy.
6	ACTION SHOULD BE TAKEN The court has not had the benefit of independent opinion as to whether the arrangements in this or indeed other trials, adequately protects patients when the conflict of interest identified above arises. It would seem prima facie to create a potential risk to lives, but the MHRA would seem to be the appropriate body to make a judgment on this matter. It is understood that the adverse reaction has already been reported to the MHRA and that new drug guidance has been issued. If any action is required the MHRA may choose to communicate that to the hospital, pharmaceutical company and/or investigator, who are copied into this report, as they may be in positions to take further actions to prevent future deaths.

7	**YOUR RESPONSE** You are under a duty to respond to this report within 56 days of the date of this report, namely by 9th August 2017. I, the coroner, may extend the period. Your response must contain details of action taken or proposed to be taken, setting out the timetable for action. Otherwise you must explain why no action is proposed. If you require any further information or assistance about the case, please contact the case officer, [redacted]
8	**COPIES and PUBLICATION** I have sent a copy of my report to the following Interested Persons: [redacted] *At King's College Hospital:* The Research Ethics Committee [redacted] Consultant oncologist) [redacted] (study investigator) [redacted] Bristol Myers Squibb (R&D Director) I am also under a duty to send the Chief Coroner a copy of your response. The Chief Coroner may publish either or both in a complete or redacted or summary form. He may send a copy of this report to any person who he believes may find it useful or of interest. You may make representations to me, the coroner, at the time of your response, about the release or the publication of your response by the Chief Coroner.
9	[DATE] 14-6-17 [SIGNED BY CORONER]