Anti-Influenza Hyperimmune Intravenous Immunoglobulin Clinical Outcome Study (INSIGHT 006: FLU-IVIG)

A Multicenter Study of the
International Network for Strategic Initiatives in Global HIV Trials
(INSIGHT)

Sponsored by: University of Minnesota

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1 Synopsis

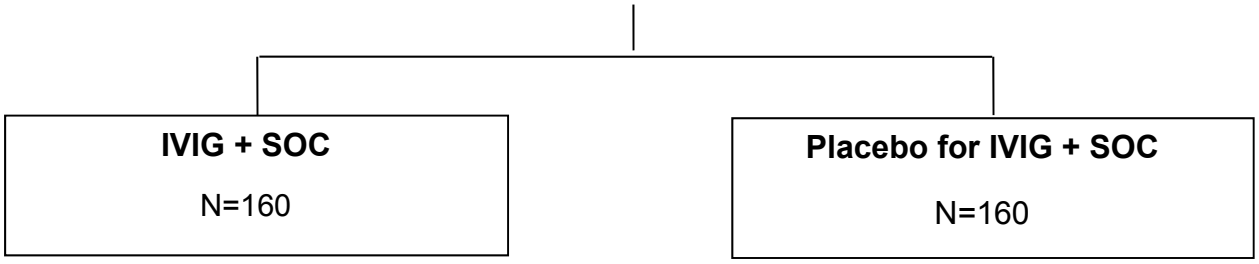
Purpose
The purpose of this randomized, double-blind, placebo-controlled trial of intravenous hyperimmune immunoglobulin (IVIG) in individuals with influenza A or B is to determine whether, when added to standard of care (SOC) treatment, administration of IVIG is superior to placebo in terms of reducing disease severity and duration.

Rationale
Influenza is responsible for 226,000 excess hospitalizations and 30,000-50,000 deaths each year in the United States alone. The number of deaths is estimated to exceed 500,000 worldwide. Despite treatment with currently available antivirals, considerable morbidity and mortality occur due to influenza. IVIG has demonstrated promising efficacy in several preliminary studies.

Design
FLU-IVIG is a randomized, double blind, placebo-controlled, multicenter, international clinical trial. Hospitalized patients with a National Early Warning[1] (NEW) score of 2 or greater will be randomized in a 1:1 allocation to receive either IVIG plus standard of care (SOC) therapy or placebo for IVIG (a comparable volume of normal saline) plus SOC, and will then be followed for 28 days. A total of 320 adult patients will be randomized over multiple influenza seasons.

Figure 1: FLU-IVIG Design

Hospitalized Adults with Influenza A or B



Endpoints
The primary endpoint is an ordinal outcome at Day 7 that has 6 mutually exclusive categories:

1. death;
2. hospitalization in the intensive care unit (ICU);
3. non-ICU hospitalization, requiring supplemental oxygen;
4. non-ICU hospitalization, not requiring supplemental oxygen;
5. not hospitalized, but unable to resume normal activities; or
6. not hospitalized with full resumption of normal activities.

Other endpoints include:

- Change from baseline to Day 3 in NEW score
- The ordinal primary outcome assessed at Days 1-7, 14 and 28
- Number of days hospitalized
- Composite of mortality or hospitalization at Days 7, 14 and 28
- Requirement for invasive mechanical ventilation or admission to the ICU (among those not enrolled from the ICU)
- Percent of patients shedding virus at Day 3
- Hemagglutination Inhibition (HAI) antibody titer changes through Day 7
- Grade 3 and 4 adverse events
- Serious adverse events
- Percent of patients developing bronchitis, pneumonia or other complications through Day 28
- Mortality

Inclusion Criteria

1. Signed informed consent
2. Age ≥ 18 years of age
3. Locally determined positive influenza test (by PCR or other nucleic acid testing, or by rapid Ag) from a specimen obtained within 2 days prior to randomization
4. Onset of illness no more than 7 days before randomization, defined as when the patient first experienced at least one respiratory symptom or fever
5. Hospitalized (or in observation unit) with influenza, with anticipated hospitalization for more than 24 hours.
6. For women of child-bearing potential: willingness to abstain from sexual intercourse or use at least 1 form of hormonal or barrier contraception through Day 28 of the study
7. Willingness to have blood and respiratory samples obtained and stored
8. NEW score ≥ 2 at screening (see Table 3)

Exclusion Criteria

1. Women who are pregnant or breast-feeding
2. Prior treatment with any investigational drug therapy within 30 days prior to screening
3. History of allergic reaction to blood or plasma products (as judged by the site investigator)
4. Known IgA deficiency

5. A pre-existing condition or use of a medication that, in the opinion of the site investigator, may place the individual at a substantially increased risk of thrombosis (e.g., cryoglobulinemia, severe refractory hypertriglyceridemia, or clinically significant monoclonal gammopathy)
6. Presence of any pre-existing illness that, in the opinion of the site investigator, would place the individual at an unreasonably increased risk through participation in this study
7. Patients who, in the judgment of the site investigator, will be unlikely to comply with the requirements of this protocol
8. Medical conditions for which receipt of a 500 mL volume of intravenous fluid may be dangerous to the patient (e.g., decompensated congestive heart failure)
9. Receiving extracorporeal membrane oxygenation (ECMO)
10. Suspicion that infection is due to an influenza strain or subtype other than A(H1N1)pdm09, H3N2, or influenza B (e.g., H5N1, H7N9)

Procedures

Hospitalized patients with a locally determined positive influenza test will be assessed for their eligibility. Eligible patients who consent to the trial will be randomized. Administration of the assigned treatment will commence on the day of randomization. Participants will be given a single infusion of IVIG or matching placebo at a dose of 0.25 g/kg (up to a maximum of 24.75 g, corresponding to approximately 100 kg actual body weight) in a total volume of 500 mL over a period of approximately 2 hours.

Nasopharyngeal swabs will be obtained on Days 0 and 3 for central determination of molecular influenza viral loads by reverse transcription polymerase chain reaction (RT-PCR). Blood will be drawn prior to infusion and on Days 1, 3 and 7 for measurement of HAI titer levels and for storage.

The primary clinical outcome will be assessed on Day 7. Participants will be followed for other clinical outcomes through Day 28.

2 Background and Rationale

2.1 Influenza

Despite vaccines and antivirals such as oseltamivir, influenza is responsible for 226,000 excess hospitalizations and 30,000-50,000 deaths each year in the United States alone. The number of deaths is estimated to be over 500,000 worldwide.[2] These complications occur against an even wider spectrum of acute self-limited illness that annually accounts for substantial morbidity (e.g., days lost from school or employment) in both the developed and the developing world. Better treatments for influenza at all stages of severity are needed.

Following the sudden and unexpected emergence of A(H1N1)pdm09 influenza virus, initial reports suggested a high mortality rate.[3,4] More recent statistics suggest a mortality rate that is similar to seasonal influenza. In 2009, the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), taking advantage of the geographic location of its sites and expertise in conducting international trials, launched 2 international protocols for observational cohort studies to estimate rates of morbidity and mortality and to examine predictors of the severity of A(H1N1)pdm09 infection.[5] One of these protocols, FLU 003, initially enrolled patients hospitalized with a presumptive or definitive diagnosis of A(H1N1)pdm09; in the other study (FLU 002), patients seen as outpatients who had influenza-like illness were enrolled. In 2010, when it became clear that A(H1N1)pdm09 was not always the dominant virus in many locations, the protocols were modified to enroll individuals with all subtypes of seasonal influenza A virus no matter what the dominating subtype was. In 2011, the protocols were further expanded to include influenza B. This INSIGHT cohort study provides some of the best data available to estimate rates of morbidity and mortality from influenza among patients in many different geographic locations around the world.

Data from FLU 003 were used to inform the design of the proposed study. Among participants enrolled in FLU 003, 333 with confirmed influenza by central PCR testing were enrolled within 7 days after the onset of influenza symptoms and had a baseline NEW score of at least 2. The status of these 333 participants on Day 7 following enrollment was as follows:

Table 1: Status of 333 Participants on Day 7 in FLU 003

Status on Day 7	No.	Percent
Died	6	1.8
Intubated or on ECMO	12	3.6
Hospitalized, on supplemental oxygen	52	15.6
Hospitalized, not on supplemental oxygen	47	14.1
Out of hospital, not returned to normal	130	39.0
Out of hospital, returned to normal activities	86	25.8

2.2 Immunotherapy

The statistics from the INSIGHT FLU 003 study confirm the substantial morbidity and health care burden associated with influenza, and the need for better treatments. One potential therapeutic strategy involves the use of hyperimmune intravenous immunoglobulin (IVIG) that is prepared either from convalescent plasma from patients with documented influenza or from volunteers previously vaccinated for influenza.

Influenza-convalescent human blood products were used to treat Spanish influenza. Luke et al described the results of 8 studies of transfusion of influenza-convalescent blood products conducted in 1918-1919.[6] None of the studies were randomized trials. Overall, 336 seriously ill patients were treated with convalescent serum, plasma or whole blood and 1,219 patients served as controls. Pooled mortality for treated patients and controls was 16% and 37%, a 57% relative difference. Absolute differences in mortality ranged from 8% to 26% among the 8 studies. Of the 8 studies, two compared early (within 4 days of pneumonia complications) and late treatment (more than 4 days after pneumonia complications) with controls. In both studies the benefit was restricted to those treated early (32% vs. 60% vs. 43% mortality for early, late and control patients in one study and 14% vs. 40% vs. 43% in the other study). The studies lacked methodological rigor but suggested that mortality could be substantially reduced with convalescent serum if introduced relatively early in the course of disease.

A non-randomized study was conducted in Hong Kong; 93 patients, aged >18 years with severe A(H1N1)pdm09 infection requiring intensive care, were recruited by 7 hospitals.[7] All participants were offered treatment with 500 mL convalescent plasma that was collected from patients recovering from influenza, and that had a neutralizing A(H1N1)pdm09 antibody titer of >1:160. Twenty individuals (21.5%) agreed to receive the plasma treatment, and 73 declined. All participants received standard antiviral treatment and other supportive medical care. Clinical outcomes were compared in the patients treated with plasma with those who declined plasma treatment as the "untreated" controls. Mortality in the treatment group was significantly lower than in the control group (20.0% vs. 54.8%; P = .01). The adjusted odds ratio (OR) for death was 0.20 (95% CI: 0.06-0.69). No adverse effects to the treatment were reported.

A multi-center prospective double-blind randomized controlled trial of a hyperimmune intravenous immunoglobulin (H-IVIG) versus normal IVIG was also conducted in Hong Kong.[8] Convalescent plasma from patients who recovered from the 2009 pandemic influenza infection was made into an immunoglobulin product (H-IVIG). Patients with severe A(H1N1)pdm09 infection on standard antiviral treatment requiring intensive care and ventilatory support were randomized at 5 hospitals in Hong Kong to receive H-IVIG or normal IVIG. Thirty-five individuals were randomized to receive H-IVIG (17 patients) or IVIG (18 patients). One of the participants assigned H-IVIG was excluded because of refusal to provide serial nasopharyngeal sampling and blood taking. Overall mortality was similar: 5 (29.4%) participants assigned H-IVIG died and 4 (23.5%) participants assigned IVIG died. However, H-IVIG treatment was associated with significantly lower day 5 and 7 post-treatment viral load when compared to the control (p=0.04 and p=0.02 respectively). A subgroup analysis suggested that there was a beneficial effect of H-IVIG on mortality among participants treated within 5 days

of symptom onset (0/12 deaths on H-IVIG versus 4/10 deaths on IVIG), although the opposite was suggested for those with symptoms for more than 5 days (5/5 deaths on H-IVIG and 0/7 deaths on IVIG). The authors indicated that no adverse effects related to treatment were reported.

Over the years various case reports and small case series of the use of IVIG and convalescent plasma for the treatment of influenza have been reported. Gordon et al report the results for 5 patients with A(H1N1)pdm09 infection treated with IVIG as potential salvage therapy. In 3 of the 5 patients IVIG therapy was associated with improvement; the other 2 patients had significant respiratory deterioration.[9] Zhou et al reported the use of convalescent plasma for the treatment of H5N1 influenza in a single patient who recovered.[10] In the absence of any controls, it is difficult to attribute any benefit or risk to the treatments used in these investigations.

Multiple studies in animals and humans conducted in the Soviet Union reported that convalescent plasma, serum and intravenous immune globulin were efficacious in the treatment of influenza pneumonia; however, these studies were small, often not randomized, and had other methodological concerns.[11,12,13,14,15,16] A recent study of immunodeficient mice homozygous for the *scid* mutation found that prophylactic passive administration of hyperimmune IVIG increased survival of mice that were challenged with pH1N1.[17]

A number of other viral diseases have also been treated with antibody preparations with variable results. These antibody preparations are generally given as IVIG. Curative treatment with IVIG is rare. Red blood cell aplasia caused by parvovirus B19 infection is the only recognized viral infection for which treatment with IVIG may eradicate the infection.[18,19] However, there is considerable evidence that immune globulin preparations may modify the natural history of viral diseases. These are summarized below.

- Cytomegalovirus (CMV): CMV enriched immune globulin preparations have shown benefit when used in combination with ganciclovir in the treatment of CMV pneumonia.[20] This immune globulin preparation is also utilized in the treatment of ganciclovir-resistant CMV infections.

- Respiratory Syncytial Virus (RSV): In adult bone marrow transplant (BMT) patients with RSV pneumonia, combination therapy using aerosolized ribavirin and standard IVIG (500 mg/kg every other day for 12 days) for the treatment had a 22% mortality rate, compared to a historical mortality rate of 70%.[21] In pediatric BMT patients with RSV pneumonia, patients treated with combination aerosolized ribavirin and RSV antibody enriched IVIG (RespiGam®) had a 9.1% mortality rate, compared with a historical 50-70% mortality rate of such patients given ribavirin alone.[22]

- Vaccinia Virus: Certain complications of vaccination with the vaccinia virus (smallpox vaccine) are treated with vaccinia immune globulin (VIG). These included generalized vaccinia, eczema vaccinatum, and progressive vaccinia. There have been no controlled trials of the efficacy of VIG. However, anecdotal

experience suggests that treatment with VIG for these conditions is beneficial, and is now considered the standard of care (SOC).[23]

- Hepatitis A: IVIG has also been shown useful in hepatitis A. Persons who have been recently exposed to hepatitis A and who have not been previously vaccinated with hepatitis A are recommended to receive standard IVIG as post-exposure prophylaxis. This is based on data that showed IVIG, when administered within 2 weeks following an exposure to hepatitis A, is greater than 85% effective in preventing hepatitis A.[24] IVIG can also attenuate the clinical expression of hepatitis A infection when given later in the incubation period.[25] Standard IVIG is used because it does contain sufficient anti-hepatitis A antibodies.

- Hepatitis B: For patients with hepatitis B and cirrhosis undergoing orthotopic liver transplant, hepatitis B hyperimmune IgG is given pre-operatively and post-operatively to prevent reinfection with hepatitis B. This has been shown to be 50-85% effective in preventing recurrence of hepatitis B in the transplanted liver.[26]

- Rabies: Rabies hyperimmune IgG is the standard recommended therapy after exposure to the rabies virus/rabid animal.[27]

- Argentine Hemorrhagic Fever: Convalescent plasma from survivors is the SOC and has been shown to reduce mortality from 50% to 4% if therapy is initiated within 8 days after disease onset.[28]

- Severe Acute Respiratory Syndrome (SARS): Convalescent human plasma may have efficacy in the treatment of SARS.[29]

- In a recent overview of studies of convalescent plasma and hyperimmune immunoglobulin convalescent plasma appeared to be safe and reduced mortality when used to treat severe respiratory infections of viral aetiology.[30]

2.3 IVIG Pilot Study

A pilot study (INSIGHT 005: FLU-IVIG Pilot) was conducted to inform the dosing requirements in this study.[31] The primary purpose of the randomized, double-blind pilot study was to determine the pharmacokinetic (PK) profile of an anti-influenza IVIG preparation and to assess whether antibody levels observed following IVIG transfusion were similar to those predicted. In the pilot study, randomization, blinding and study procedures were also evaluated. Thirty-one patients were randomized in the FLU-IVIG Pilot, 16 to IVIG and 15 to placebo for IVIG. Key findings are:

- At one hour post-infusion, targeted HAI titer levels were achieved in 100% of patients for A/California/07/2009 H1N1pdm09 (1:64), 100% of patients for A/Texas/50/2012/ H3N2 (1:32), and 94% of patients for B/Massachusetts/02/2012 (1:16).

- HAI titer levels for patients with H1N1pdm09 (55% of patients), differed significantly between the IVIG and placebo groups through Day 3 of follow-up. Due to natural immunity treatment differences in HAI titer levels diminished with longer follow-up. There was no between-group difference in HAI titer levels after Day 3.

- Increases in HAI titers were smaller for influenza B than influenza A.

- Two of 31 patients did not receive the full dose of IVIG/placebo. One patient refused the infusion following randomization, and the infusion for a second patient was interrupted due to anxiety and a subjective feeling of dyspnea. No safety concerns were identified in the study.

- Blinding appears to have been maintained. At the end of the trial, patients and clinical staff who assessed outcomes were asked to guess their assignment and this indicated that the blinding had been achieved.

The FLU-IVIG Pilot study included outpatients and other patients who did not meet the strict eligibility criteria of this study. Of the 31 patients randomized, 16 (52%) would meet the eligibility criteria of the proposed study. Since the data collection plans for this study and the FLU-IVIG Pilot studies are similar, the clinical and virologic outcomes for these 16 patients will remain blinded and will be used to supplement the newly enrolled patients in INSIGHT 006.

2.4 Potential Risks

2.4.1 Risks of IVIG

Like the FLU-IVIG Pilot, the IVIG used in this study will be manufactured in the same manner and to the same standards as commercially available (non-influenza antibody enriched) IVIG. This includes screening for blood-borne pathogens and manufacturing steps that include solvents/detergents to inactivate any viruses. There are no anticipated unique risks to an anti-influenza antibody enriched IVIG; therefore the risks are anticipated to be the risks of standard IVIG preparations. Common risks include fever, rash, hives, or headache. Other more serious risks are rare and include serious allergic reactions including anaphylaxis, hemolysis, and aseptic meningitis. As IVIG is made from human plasma, transmittable viral infections such as hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) are a potential risk, although steps are taken to screen for and inactivate such pathogens. In addition, there is a theoretical risk, although low, that IVIG administration may be capable of transmitting other known or unknown infectious agents other than viruses, such as infectious prions (e.g., the agent of Creutzfeldt-Jakob disease).

Immune globulin administration may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. Renal dysfunction, acute renal failure, and osmotic nephropathy may occur with immune globulin intravenous products in predisposed patients. Renal dysfunction and acute failure occur more

commonly in patients receiving IVIG products containing sucrose. The influenza IVIG preparation used in this study does not contain sucrose.

Although rare, transfusion-related acute lung injury (TRALI) may occur with IVIG therapy and is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever.

There are case reports of pulmonary emboli occurring after administration of IVIG and plasma therapy, although definitive studies assessing risk are lacking.[32] In one series 5 of 10 patients critically ill with A(H1N1)pdm09 were shown to have pulmonary emboli.[33] This high percentage has not been shown in other H1N1 series, and pulmonary emboli have been shown to develop in approximately 10-15% of critically ill adults.[34] However, the potential risk of pulmonary embolism exists. Other thrombotic events, including myocardial infarction, cerebral vascular accident, and deep vein thrombosis may also occur.

2.4.2 Risks Associated with Procedures

The primary risk of nasopharyngeal (NP) swabs is local discomfort or gagging. Rarely, there can be local bleeding from the nasal mucosa, which is controlled with local measures such as pressure or packing with gauze.

The risks of having blood taken typically include short-lasting pain, bleeding, bruising, lightheadedness, fainting and, rarely, infection or a blood clot where the needle enters the body.

2.5 Clinical Endpoint Considerations

There are no established clinical endpoints for evaluating the clinical efficacy of influenza treatments. Furthermore, as noted in a guidance document from the Food and Drug Administration (FDA), no study has definitively demonstrated substantial clinical efficacy in patients with serious influenza who are hospitalized.[35] A number of possible clinical and virologic endpoints have been proposed for antiviral treatments.[36] These include death, progression to respiratory failure, continued clinical instability, prolonged hospitalization, and return to premorbid status. Each of these outcomes will be assessed in INSIGHT 006.

As a general requirement, the endpoint for a clinical trial should be clinically relevant, ascertainable in an unbiased manner for both treatment groups and occur with sufficient frequency to make a study feasible. For example, mortality is a relevant clinical outcome but it occurs in too small a percent of patients to use it as the primary endpoint; sample size would be prohibitive. In FLU 003, mortality after 14 days was less than 3% for patients who were enrolled while in the general hospital ward[37]; for potentially eligible patients for this study, mortality was less than 2% at Day 7 in FLU 003 (see section 2.1). On the other hand, sample size would be smaller for a virologic outcome as compared to a clinical endpoint but viral shedding is not an established surrogate marker for clinical disease. It is important that the outcome used capture the patient's clinical status during follow-up.

With these considerations, for the primary endpoint of the proposed study, we defined an ordinal outcome that is based on the patient's status at Day 7 of follow-up. An ordinal outcome has been used in other studies of seriously ill patients[38]; such an outcome will likely have greater statistical power than a binary clinical outcome assessed at Day 7 since it uses more information. Day 7 was chosen as a time point for the primary comparison because, based on the FLU-IVIG Pilot, differences between treatment groups in HAI titer levels are greatest in the first few days after treatment with IVIG. Also, measures of clinical status at later time points could reflect the impact of co-morbidities instead of influenza and dilute any treatment difference. Because of the uncertainty about the clinical endpoint to use in studies of hospitalized patients with influenza, and because of the importance of follow-up for a longer period of time than 7 days, multiple other clinical outcomes and a virologic endpoint will also be assessed as secondary endpoints over the planned 28 day follow-up period.

2.6 Study Product

For this study, the FLU-IVIG was manufactured by Emergent BioSolutions, Winnipeg, Canada (formerly Cangene) under contract to the United States National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), using high titer plasma collected from volunteers. Emergent BioSolutions also manufactured the product used in the pilot study (INSIGHT 005: FLU-IVIG Pilot). The IVIG product used in this trial is manufactured according to Good Manufacturing Practices (GMP) from human plasma collected under IND at sites that are FDA-registered or licensed to perform this function. Based on the current Investigator's Brochure (Version 5.0), the plasma used in this IVIG product meet the following criteria prior to being used for manufacture:

- Negative Aniti-HIV 1 / 2
- Negative Anti-HTLV 1 / 2
- Negative Anti-HCV
- Negative HBsAg
- Negative serologic test for syphilis
- Negative HIV NAT
- Negative HCV NAT
- Negative WNV NAT
- Negative Hepatitis A virus NAT
- Negative Hepatitis B virus NAT
- Negative Parvovirus B19 NAT

Any updates to the criteria will be documented in the next version of the Investigator's Brochure.

All tests are performed by commercially available assays.

The lots of IVIG are tested at manufacture and periodically (at 3, 6, 9, 12, 18, 24, 36, and 48 months post-manufacture) for contemporary strains of influenza (as defined by the strains recommended by the WHO for the seasonal influenza vaccine). IVIG is manufactured in batches, and lot-to-lot variations in antibody titers may occur. The

strain-specific HAI results by lot are included in the Investigator's Brochure (IB), however, it is anticipated that the IVIG to be used in this study has the following average HAI titers:

- A/H1N1 = 1:640
- A/H3N2 = 1:640
- B = 1:160

If any new strains of influenza emerge through a season, additional HAI testing will be conducted against the new strain, when able, to document expected activity towards the new strain.

The anticipated HAI titer levels in participants following infusion were estimated as follows. The Vz (volume of distribution) of IVIG is approximately 0.05 L/kg, which is approximately the plasma volume.[39] At the proposed dose of 0.25 g/kg, a 70 kg subject would receive 350 mL of influenza IVIG (with a minimum HAI titer of 1:640 for H3N2 and 1:160 for influenza B based on the above results). Thus, in a plasma volume of 3.5 L (0.05 L/kg) the minimum resultant HAI titer is estimated to be approximately 1:64 for H3N2 and 1:16 for influenza B.

At the proposed dose, theoretically the following HAI titers would be expected in the recipient (assuming no pre-existing immunity):

- A/ H1N1pdm09 = 1:64
- A/ H3N2 = 1:64
- B= 1:16

Data from seasonal inactivated vaccines indicate that inducing an HAI titer > 1:40 (sero-protection) in immunized individuals should be at least 70% effective in preventing influenza infection.[40,41] An overview of 12 studies by de Jong et al. found that the median HAI titer protecting 50% of those vaccinated against the virus was 1:28.[42] However, it must be emphasized that protective pre-exposure prophylactic titers and post-exposure disease-modification titers are distinct concepts that do not necessarily harmonize, and the HAI titer actually needed for modifying favorably the course of an established influenza infection is not clear.

Rockman et al demonstrated in an H5N1 model in ferrets that achieving an HAI titer of 1:8 with a hyperimmune IVIG without any other antivirals was sufficient in preventing death if given early in the illness (during fever), and in delaying death if given at the onset of severe disease.[43]

In the non-randomized plasma treatment study that showed significant mortality benefit associated with convalescent plasma infusion, the HAI in recipients was estimated to be 1:11.7

3 Methodology

3.1 Study Design

INSIGHT 006: FLU-IVIG is a multicenter, double-blind, randomized, placebo-controlled clinical trial comparing treatment with hyperimmune intravenous immunoglobulin (IVIG) versus placebo in hospitalized patients with locally confirmed influenza A or B who have a NEW score ≥ 2. For participants in both assigned treatment groups, the randomized treatment will be administered in addition to SOC treatment. The study will be blinded to participants and to clinical staff other than the site pharmacist.

Study participants will begin to be enrolled in the 2014-2015 influenza season. Enrollment will continue in subsequent influenza seasons until the required sample size is achieved.

3.2 Treatment

The dispensing of study medication will be performed by a site pharmacist unblinded to the treatment assignment. The pharmacist at each clinical site will use normal saline that is approved by their hospital formulary.

Participants assigned to the placebo arm will receive a 500 mL bag of normal saline without any modifications. For those assigned to IVIG, the pharmacist will prepare a bag containing IVIG at a dose of 0.25 g/kg of actual body weight, to a maximum of 24.75 g IVIG (approximately 100 kg), plus as much saline as is needed to reach a total of 500 mL. Detailed instructions for the pharmacist are in the *INSIGHT FLU-IVIG Pharmacy Manual* and the Investigator's Brochure (IB) for IVIG.

It is recognized that the presence of IVIG in normal saline will produce a yellowish coloration and some turbidity to the saline base that will vary depending upon the amount of IVIG product involved. To knowledgeable staff or participants, this appearance could potentially unblind the study medication at the time of administration. Nonetheless, a reasonable effort will be undertaken to keep both the non-pharmacist staff at the clinical site and the study participant blinded to the treatment administered without interfering with safe intravenous infusion policies that may exist at a given institution.

Following procedures used in INSIGHT 005: FLU-IVIG Pilot, in which the blind was effectively maintained, site pharmacists will be instructed to place a colored sleeve or other suitable covering over the 500 ml bag to mask the color of the contents therein, a process similar to what is occasionally done to shield photosensitive medications from light degradation.

In the case of a medical emergency, at the request of the site investigator, the site's study pharmacy staff can provide the participant's unblinded treatment assignment.

All participants will receive SOC treatment. This will be determined by their treating clinician and will not be dictated by this protocol. It is anticipated that SOC will include

an antiviral effective against the circulating strain of influenza. It is further anticipated that this will be oseltamivir in most cases, but use of other antivirals such as zanamivir or peramivir is permitted and will be left to the discretion of the treating clinician.

3.3 Study Objectives

3.3.1 Primary Objective

The primary objective is to compare the clinical status of patients in the IVIG and placebo groups at 7 days of follow-up using an ordinal outcome with 6 clinical states. Specifically, patients will be categorized into one of the following 6 mutually exclusive categories on Day 7:

1) death;
2) hospitalization in the intensive care unit (ICU);
3) non-ICU hospitalization, requiring supplemental oxygen;
4) non-ICU hospitalization, not requiring supplemental oxygen;
5) not hospitalized, but unable to resume normal activities; or
6) not hospitalized with resumption of normal activities.

3.3.2 Secondary Objectives

a. To compare participants in the IVIG and placebo groups for the following secondary outcomes:
   - Change from baseline to Day 3 in NEW score
   - The ordinal primary outcome assessed at Days 1-7, 14 and 28
   - Number of days hospitalized
   - Composite of mortality or hospitalization at Days 7, 14 and 28
   - Requirement for invasive mechanical ventilation or admission to the ICU (among those not enrolled from the ICU)
   - Mortality
   - Complications of influenza such as bronchitis and pneumonia
   - Percent of patients shedding virus at Day 3

b. To compare the IVIG and placebo groups for HAI titer levels at Days 1, 3 and 7.

c. To compare the IVIG and placebo groups for major clinical outcomes in subgroups defined by the following characteristics measured at baseline:
   - Age
   - Gender
   - Race/ethnicity
   - Geographic region (United States, Europe, South America, Australasia)
   - Duration of symptoms prior to enrollment
   - Influenza subtype
   - Type of hospital ward at time of enrollment
   - Production lot of IVIG

d. To compare the safety and tolerability of the FLU-IVIG and placebo group for:

- Number and percent with grade 3 or 4 adverse events (AEs)
- Number and percent with serious adverse events (SAEs)
- Number and percent with early termination of study treatment

e. To relate viral load and HAI changes to clinical outcomes and assess whether these potential surrogate markers explain any clinical endpoint difference found.

3.4 Endpoints

The primary endpoint is an ordinal outcome at Day 7 that has 6 mutually exclusive categories:

1. death;
2. hospitalization in the intensive care unit (ICU);
3. non-ICU hospitalizion, requiring supplemental oxygen;
4. non-ICU hospitalization, not requiring supplemental oxygen;
5. not hospitalized, but unable to resume normal activities; or
6. not hospitalized with full resumption of normal activities.

Other endpoints include:

- Change from baseline to Day 3 in NEW score
- The ordinal primary outcome assessed at Days 1-7, 14 and 28
- Number of days hospitalized
- Composite of mortality or hospitalization at Days 7, 14 and 28
- Among those not enrolled in the ICU, requirement for invasive mechanical ventilation or admission to the ICU
- Percent of patients shedding virus at Day 3
- HAI antibody titer changes through Day 7
- Grade 3 and 4 adverse events
- Serious adverse events
- Percent of patients developing bronchitis, pneumonia or other complications through Day 28
- Mortality

3.5 Randomization

Eligible patients will be randomized in a 1:1 ratio to receive either IVIG + SOC or placebo + SOC. Randomization will be stratified by clinical site.

3.6 Sample Size and Statistical Considerations

The planned sample size for the trial is 320 randomized patients. Sixteen of these 320 patients will come from the FLU-IVIG Pilot. A sample size re-estimation will be made after approximately 150 patients have been enrolled.

The following assumptions were made in estimating the required sample size for the trial:

a. The primary analysis will be intention to treat with a proportional odds model that includes indicators for treatment group and indicators for whether the patient was enrolled in the ICU and required oxygen at the time of

randomization. The model will be stratified by geographic region (United States, Europe, South America and Australasia).

b. Type 1 error is 0.05 (2-sided) and power =0.80.

c. Patients will be equally allocated to IVIG or placebo.

d. The clinical status of patients in the control arm at Day 7 will be similar to patients enrolled in the hospital in FLU 003 (see section 2.1 and table below). The estimates from FLU 003 are based on 333 hospitalized patients who were enrolled 7 or fewer days after onset of influenza symptoms and who had a NEW score of 2 or greater at the time of enrollment.

e. In FLU 003, approximately 64-65% of patients were out of the hospital on Day 7 (sum of 39.0% and 25.8% in table). We assumed that for patients given IVIG this percent could be increased to 74% (about 10 percentage points). We assumed this same proportional improvement (an odds ratio of approximately 1.6) would apply to other category cutpoints on the ordinal scale (an underlying assumption of the proportional odds model). If that were the case, the percentages in each clinical state in the IVIG group that would be realized are shown Table 2.[44]

f. Based on the FLU-IVIG Pilot, we expect minimal non-adherence to IVIG and missing data at Day 7.

Table 2: Difference that Can Be Detected in the Day 7 Ordinal Outcome

Power = 80%, Alpha = .05 (2-sided) and Sample Size = 320

	Day 7 Outcome (%)	
Hierarchical Outcome	**Placebo**	**IVIG**
Death	1.8	1.0
In ICU	3.6	2.1
Non-ICU hospitalization, on O2	15.6	9.9
Non-ICU hospitalization, not on O2	14.1	10.3
Not back to normal activities	39.0	38.4
Resumed normal activities	25.8	38.2
Odds ratio		1.77

In summary, 320 patients (160 assigned IVIG and 160 assigned placebo) will be randomized. An odds ratio will be computed as a summary measure of the treatment effect. For the above table, this odds ratio is 1.77. This can be interpreted as the average shift over the entire ordinal outcome scale caused by IVIG. An odds ratio greater than one corresponds to a more favorable response for treatment with IVIG as compared to placebo. With the proportional odds model this odds ratio is assumed to be the same for all possible ways of collapsing the 6-category scale into a better versus worse category (e.g., the odds ratio is 1.77 for out of hospital versus in hospital, not in ICU or death versus death or in ICU, etc).

3.7 Availability of IVIG Lots

Study product will come from at least 4 lots of IVIG. The first lot, the IVIG remaining in inventory from the FLU-IVIG Pilot study, is sufficient for approximately 10-15 patients assigned to IVIG. The second lot became available for use in September 2014, and it is estimated that it will provide sufficient IVIG to treat 55 patients with IVIG (i.e., to randomize approximately 110 patients) at the same dose used in the FLU-IVIG Pilot. The third lot became available in September 2015.

A fourth lot of IVIG is being prepared and is expected to become available in September 2016, allowing approximately 470 patients to be enrolled if necessary. This will be determined following a sample size re-estimation that is carried out after approximately 150 participants have been enrolled. A decision on the need for additional lots will consider the time requirements for collecting plasma and manufacturing IVIG.

3.8 Participant Selection

As a general guideline, individuals who are considered for enrollment should be able, in the clinician's opinion, to adhere to the protocol (i.e., be willing to accept and adhere to the data and specimen collection schedule and the assigned treatment).

3.8.1 Inclusion Criteria

1. Signed informed consent
2. Age ≥ 18 years of age
3. Locally determined positive influenza test (by PCR or other nucleic acid test, or by rapid Ag) from a specimen obtained within 2 days prior to randomization
4. Onset of illness no more than 7 days before randomization, defined as when the patient first experienced at least one respiratory symptom or fever
5. Hospitalized (or in observation unit) with influenza, with anticipated hospitalization for more than 24 hours.
6. For women of child-bearing potential: willingness to abstain from sexual intercourse or use at least 1 form of hormonal or barrier contraception through Day 28 of the study
7. Willingness to have blood and respiratory samples obtained and stored
8. NEW score ≥ 2 at screening (see Table 3)

3.8.2 Exclusion Criteria

1. Women who are pregnant or breast-feeding
2. Prior treatment with any investigational drug therapy within 30 days prior to screening
3. History of allergic reaction to blood or plasma products (as judged by the site investigator)
4. Known IgA deficiency
5. A pre-existing condition or use of a medication that, in the opinion of the site investigator, may place the individual at a substantially increased risk of thrombosis (e.g., cryoglobulinemia, severe refractory hypertriglyceridemia, or clinically significant monoclonal gammopathy)
6. Presence of any pre-existing illness that, in the opinion of the site investigator, would place the individual at an unreasonably increased risk through participation in this study
7. Patients who, in the judgment of the site investigator, will be unlikely to comply with the requirements of this protocol
8. Medical conditions for which receipt of a 500 mL volume of intravenous fluid may be dangerous to the patient (e.g., decompensated congestive heart failure)
9. Receiving extracorporeal membrane oxygenation (ECMO)
10. Suspicion that infection is due to an influenza strain or subtype other than A(H1N1)pdm09, H3N2, or influenza B (e.g., H5N1, H7N9)

Table 3: National Early Warning Score (NEWS)

National Early Warning Score (NEWS)*

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

*The NEWS initiative flowed from the Royal College of Physicians' NEWS Development and Implementation Group (NEWSDIG) report, and was jointly developed and funded in collaboration with the Royal College of Physicians, Royal College of Nursing, National Outreach Forum and NHS Training for Innovation.

Please see next page for explanatory text about this chart.

Royal College of Physicians

NHS Training for Innovation

3.9 Study Plan

3.9.1 Screening and Baseline

Consenting participants will have the following screening/baseline information and measurements collected.

<u>Within 2 days prior to randomization</u>

- Demographics and medical history
- For women of child-bearing potential, a pregnancy test
- Assessment of NEW score
- Use of antiviral treatment
- Laboratory confirmation of influenza
- Clinical data
- Local labs:
    - CBC with differential white cell count, hemoglobin, hematocrit, platelets
    - Blood chemistries: sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT/GPT, AST/GOT, total bilirubin, PTT, PT, INR

On the day of randomization (Day 0)

- Targeted symptoms
- Assessment of NEW score (if not already performed for screening on Day 0)
- Serum specimen for central lab (sufficient for 4 1-mL transport tubes, for serology testing and stored sample)
- Plasma specimen for central lab (sufficient for 4 1-mL transport tubes, for stored sample)
- Nasopharyngeal (NP) swab for quantitative PCR (1 swab in 3mL VTM)

Screening and baseline data and specimen collection requirements are summarized in tabular form in Appendix B: *FLU-IVIG Time and Events Schedule.* Details of specimen handling can be found in the *INSIGHT FLU-IVIG Laboratory Manual.*

For participants who consent to the separate INSIGHT Genomics study (INSIGHT 004), a whole blood sample will be obtained for DNA extraction to study polymorphisms in immune response genes and other genetic variants that may be associated with an increased risk of respiratory diseases due to influenza.

3.9.2 Randomization and Blinding Procedures

This study uses a placebo (normal saline) that is prepared and labeled to resemble active treatment (IVIG) by site pharmacists who are unblinded to the treatment assignment. Randomization will be performed by study personnel using procedures outlined in the *INSIGHT FLU-IVIG Protocol Instructions Manual.*

Blinding of the participant and clinical site staff will be achieved by placing a colored sleeve over the 500 mL bag that contains the IVIG plus normal saline or normal saline alone. In the event that the blind is broken for reasons of safety, this will be recorded and the study team will be notified. In that situation, every attempt will be made to minimize the number of people unblinded.

Blinding is important for assessing safety and other outcomes planned for the clinical efficacy study; therefore procedures and the ability to maintain the blind will be evaluated at the end of follow-up for each participant.

3.9.3 Storage and Administration of Study Treatment

After a site is opened for enrollment, a supply of IVIG will be provided to the clinical site pharmacy. Details for storing, labeling, and dispensing study treatment are detailed in the *INSIGHT FLU-IVIG Pharmacy Manual.*

Administration of blinded study treatment will commence as soon as possible after randomization on the day of randomization (Day 0). The study treatment will be administered in a single infusion with a total volume of 500 mL over approximately 2 hours.

3.9.4 Participant Follow-up

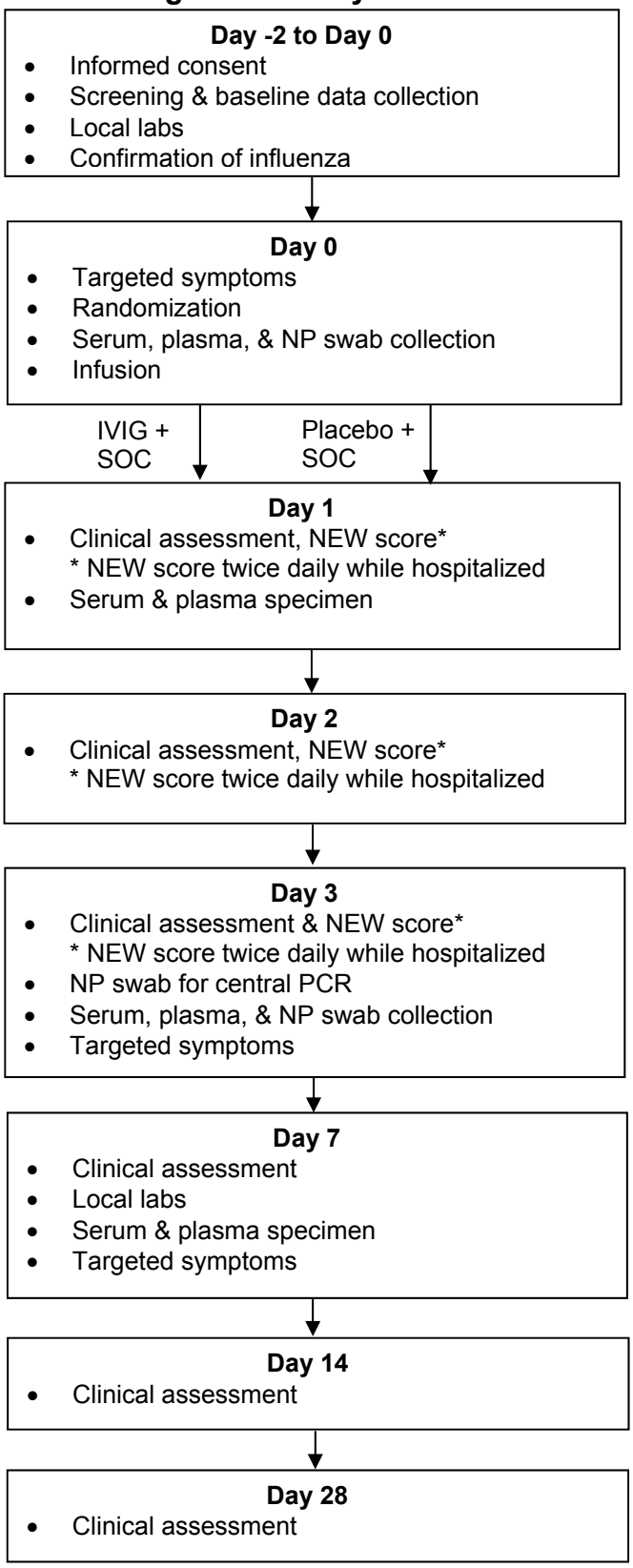
Participants will be followed through Day 28 following randomization for collection of study data. Clinical data will be collected on Days 1-3, 7, 14, and 28. For participants

who are not hospitalized, contact with the participant for the purpose of study data collection may be performed by telephone on Days 2, 14 and 28.

An NP swab for central RT-PCR testing will be obtained on Day 3. On Day 7, a local CBC and chemistry panel will be obtained. On Days 1, 3, and 7, serum and plasma samples (sufficient for 4 1-mL transport tubes of each) will be obtained for central testing of the immune response to influenza and for storage for future influenza-related research.

Follow-up data and specimen collection requirements are summarized in tabular form in Appendix B: *FLU-IVIG Time and Events Schedule.* Details of specimen handling can be found in the *INSIGHT FLU-IVIG Laboratory Manual.*

Figure 2: Study Flow Sheet



4 Assessment of Safety

4.1 Documenting, Recording, and Reporting Adverse Events and Unanticipated Problems

At each contact with the participant, information regarding adverse events and Unanticipated Problems will be elicited by appropriate questioning and examinations and will be:

- Immediately documented in the participant's medical record/source document
- Recorded on the appropriate case report form
- Reported as outlined below (e.g., IND holder, IRB, FDA)

4.2 Investigator Assessment and Reporting of Adverse Events and Unanticipated Problems

4.2.1 Adverse Event

An adverse event is any untoward or unfavorable medical occurrence in a study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with their participation in research, whether or not considered related to the research. If a diagnosis is clinically evident (or subsequently determined), the diagnosis, rather than the individual signs and symptoms or lab abnormalities, will be recorded as the AE.

4.2.2 Serious Adverse Event (SAE)

An SAE is an AE that results in one or more of the following outcomes:

- Death
- Events that are life-threatening (i.e., an immediate threat to life)
- Events requiring hospitalization or prolongation of hospitalization
- Events resulting in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital abnormalities/birth defects
- Other important medical events that may jeopardize the participant and may require intervention to prevent one of the outcomes listed above

All events meeting the above criteria are reportable as SAEs. In addition, all occurrences of TRALI (see section 2.4.1), regardless of grade, are also defined as medically important events for the purposes of this protocol, and are therefore to be reported as SAEs.

Additional details on reporting SAEs are found in the *INSIGHT FLU-IVIG Protocol Instructions Manual.*

4.2.3 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience or outcome that is:

1. Unexpected in terms of nature, severity, or frequency in relation to:

a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents; and
b. the characteristics of the population being studied; and

2. Possibly, probably, or definitely related to participation in the research; and
3. Places study participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Furthermore, a UP could be an expected event that occurs at a greater frequency in the IVIG group than placebo group. The Data and Safety Monitoring Board (DSMB) providing oversight to the study may make such an assessment based on an aggregate analysis of events. In that case, they will notify the sponsor who will in turn notify clinical site investigators who will be asked to submit the written DSMB summary report to IRBs.

4.2.4 Assessment of Severity and Causality for Adverse Events and Unanticipated Problems

The investigator will evaluate all AEs with respect to seriousness as above (see section 4.2.2) and severity (intensity or grade). AEs will be graded for severity according to the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, (also known as the DAIDS AE Grading Table; see Appendix D for the URL link).
AEs will be reported irrespective of perceived relationship to the study agent.

For specific events that are not included in the DAIDS AE Grading Table, the following generic scale is to be used:

Table 4: Generic AE Grading Scale

Grade 1	Symptoms causing no or minimal interference with usual social and functional activities
Grade 2	Symptoms causing greater than minimal interference with usual social and functional activities
Grade 3	Symptoms causing inability to perform usual social and functional activities
Grade 4	Symptoms causing inability to perform basic self-care functions, or medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
Grade 5	Events resulting in death

Causality (likelihood that the event is related to the study agent) will be assessed for SAEs and UPs. For the purposes of IND safety reporting, 'reasonable possibility' of relationship means there is evidence to suggest a causal relationship between the drug and the adverse event. Such evidence includes temporal relationship between study

agent administration and event, a known or suspected response pattern based on similar agents, and the likelihood (or lack thereof) of an alternative etiology.

Note: Causality assessment is based on available information at the time of the assessment of the event. The investigator may revise the causality assessment as additional information becomes available.

4.2.5 Reporting of Adverse Events

As noted in section 2.4.1 there are potential risks associated with taking IVIG. These risks include fever, rash, hives, headache, allergic reactions, transmitted infections, renal dysfunction/failure, TRALI and pulmonary embolism. The risk of transmitted infections is considered low because of the screening of the plasma used to make the IVIG.

Some of these risks are similar to symptoms associated with influenza. Also, it is expected that many participants will have co-morbid conditions that are associated with signs, symptoms and laboratory abnormalities that are similar to possible risks of IVIG. Thus, AEs will be collected irrespective of perceived relationship to treatment in order to compare differences between the IVIG and placebo groups.

Through 28 days of follow-up, AE data collection will be restricted to any new grade 3 or 4 AE, or previously existing AEs which have increased in severity to grade 3 or 4.

4.3 Reporting Responsibilities

4.3.1 Adverse Events

Line listings, frequency tables, and other summary AE data will be submitted to RCHSPB (via the INSIGHT Safety Office) as required for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports. These summaries will be for both treatment groups combined.

4.3.2 Serious Adverse Events

All SAEs must be reported immediately (within 24 hours of awareness) by sites to the sponsor via the INSIGHT Safety Office. Suspected unexpected serious adverse reactions (SUSARs) that result in death or are immediately life-threatening will be reported from the INSIGHT Safety Office to the NIAID Office of Clinical Research Policy and Regulatory operations (OCRPRO) and applicable regulators within 7 calendar days of receipt. All other SUSARs will be reported to OCRPRO and regulators within 15 calendar days.

4.3.3 Unanticipated Problems

Non-serious AEs that are considered UPs must also be reported on CRFs and sent to the Safety Office no later than 7 calendar days after site awareness of the event.

4.3.4 Investigator Reporting Responsibilities to Local IRB(s) and Ethics Committees (ECs)

Investigators are responsible for submitting IND Safety Reports and UP summaries that are received from the IND holder to their local IRB/EC. Investigators must also comply with all local IRB/EC reporting requirements.

4.3.5 Follow-up of Serious Adverse Events

Participants who experience SAEs are followed until the final outcome is known, even if this occurs after the end of the study follow-up at 28 days.

4.3.6 Serious Adverse Event Reporting Required by the European Union

In accordance with the EU Directive 2001/20/EC (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF), 2011/C 172/01 (CT-3) (http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf), UK SI 2004 1031 (http://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf), and subsequent revisions, and member state requirements, the sponsor, through its legal representative in Europe, will ensure that all relevant information about serious adverse events including suspected unexpected serious adverse reactions (SUSARs) is recorded and reported to the central and/or concerned member state authorities and IECs as appropriate and in compliance with requirements for expedited reporting. The study data collected will be used to construct the required reports to European authorities.

4.4 Study Deviations and Violations

Protocol deviations will be reported on a CRF and these deviations will be summarized for the protocol team and the DSMB. The protocol team will work with the site to promptly develop corrective actions as warranted.

4.5 Safety Oversight

4.5.1 Medical Monitor

A Medical Monitor will participate on the study team (see Appendix C). The Medical Monitor will be responsible for performing safety assessments as outlined above and communicate, as needed, with the IND holder.

4.5.2 Data and Safety Monitoring Board (DSMB)

A DSMB will review the study data to evaluate the safety, efficacy, study progress, and conduct of the study (see Section 6.2). Written DSMB summary reports with recommendations will be submitted to IRBs.

5 Clinical Management Issues

The following clinical management guidelines apply to both treatment groups.

5.1 Early Discontinuation of Study Treatment

Case report forms will be used to capture both the intended total dosage of study treatment as well as the dosage actually received. Reasons for early termination of study treatment will be recorded.

5.2 Study Withdrawal

A participant may be withdrawn if:

- He/she is imprisoned or involuntarily incarcerated for medical reasons
- The study is discontinued.

All patients should otherwise be followed according to protocol.

Participants may withdraw from the study at any time at their request and resume participation at any time upon re-consent. Even if a participant did not receive all or any of the assigned study treatment, or some required data or specimens cannot be collected, every effort should be made to follow participants for clinical outcomes until the end of the study.

5.3 Prohibited Medications

Participants may not receive other investigational medications during the first 7 days of follow-up.

5.4 Live Virus Vaccines

As mentioned in section 2.4.1, immune globulin administration may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. Whenever possible, vaccination with live virus vaccines should be deferred until at least three months after administration of the IVIG.

5.5 Pregnancy and Breastfeeding

Given the lack of known efficacy, and unknown potential toxicities, women are not eligible for enrollment into the study during their pregnancy or while they are breastfeeding. For women of child-bearing potential, a serum or urine pregnancy test must be performed before randomization.

5.6 Children

Given the lack of known efficacy, and unknown potential toxicities, individuals < 18 years of age are not eligible for enrollment into the study.

6 Evaluation

6.1 Data Analysis

The primary analysis will be intention to treat, comparing the outcomes of patients assigned IVIG with those assigned placebo. For the primary endpoint, the percent of patients in the following 6 categories will be compared: 1) death; 2) ICU; 3) non-ICU ward, on supplemental oxygen; 4) non-ICU ward, not on supplemental oxygen; 5) out of the hospital but normal activities have not been resumed; and 6) out of the hospital

and normal activities resumed. Patients discharged from the hospital to a rehabilitation facility will be included in category 5) above. Patients discharged from the hospital to a nursing home will also be included in category 5), unless the patient lived in a nursing home prior to admission to the hospital, in which case the patient will be characterized based on resumption of normal activities.

A proportional odds model will be used to estimate a summary odds ratio. The model will include an indicator for treatment and indicators for the patient's clinical state at entry (ICU, general ward on supplemental oxygen, general ward not on supplemental oxygen). The model will be stratified by geographic region (United States, Europe, South America and Australasia).

To supplement the overall summary odds ratio, separate odds ratios will be estimated for each dichotomized definition of improvement that can be formulated from the components of the ordinal outcome. A test for the proportionality assumption will also be made.

The following clinical secondary outcomes are of interest: 1) percent alive and out of the hospital at Day 14; 2) change in NEW score at Day 3; and 3) resumption of normal activities at Day 14. It is expected that IVIG will have a favorable effect on each of these outcomes as well as the ordinal primary outcome. Since the primary endpoint and these secondary endpoints are related and expected to be correlated, before examining each secondary endpoint separately, a single global test will be carried out using the method described by O'Brien and Pocock. [45,46] With this approach, the endpoints will be equally weighted and a single global test statistic will be determined. This single global test is expected to have greater power than the test for each endpoint separately. For example, for a common correlation among the four outcomes of 0.50, the average Z value must be 1.55 (instead of 1.96) to achieve a significance level of 0.05. The combined evidence using all four outcomes does not have to be as extreme as for a single outcome.

Time to death and time to hospital discharge will be summarized with Kaplan-Meier plots and Cox models. For time-to-event analyses, time will be measured from randomization. The comparison of NEW scores and HAI titers will be compared using analysis of covariance with the baseline score or titer as a covariate. HAI titer levels will be log-transformed and the data at each time point will be summarized as the ratio of geometric means for those assigned IVIG and placebo.

Longitudinal random effects models will also be used to summarize repeated assessments of the ordinal outcome, HAI titers and the NEW score. By collecting specific dates when patients are removed from the ICU and oxygen, discharged and resume normal activities, the ordinal outcome can be defined for a patient on each day of follow-up.

Symptoms reported and AEs will be compared for the IVIG and placebo groups and summarized using chi-square statistics. Laboratory measurements will be summarized as changes from baseline to Day 7.

Subgroup analyses for the primary and secondary outcomes will be performed to determine whether the treatment effect (IVIG versus placebo) differs qualitatively across baseline-defined subgroups. The following subgroups will be considered: age, gender, race/ethnicity, geographic region, duration of symptoms prior to enrollment, influenza subtype, enrollment in ICU versus general ward and production lot of IVIG used. For each subgroup considered, an overall test of heterogeneity of treatment effect will be constructed to assess how strong the evidence is that the treatment effect varies across the baseline subgroups.

6.2 Data Monitoring

The trial will be conducted under the direction of the FLU-IVIG study protocol team. Members of the protocol team are listed in Appendix C. The protocol team (except those who prepare the confidential analyses) and all participating investigators will be blinded to interim results. The protocol team will monitor enrollment, follow-up, and adherence to the assigned treatment as determined by the number and percent of participants who complete the infusion of blinded treatment. Follow-up data will be summarized for both treatment groups combined. The protocol team will carry out a sample size re-estimation after approximately one-half of the patients have been enrolled. For this sample size re-estimation, pooled data for the primary endpoint will be used.

The DSMB will review the study prior to initiation and every 6 months thereafter. The DSMB may convene additional reviews as necessary. After each meeting they will recommend continuing the study as planned, modifying the study, or terminating the study.

The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference. As a guideline, the Lan-DeMets spending function analog of the O'Brien-Fleming boundaries will be used to monitor the primary endpoint comparison.[47,48]

After approximately 50% of patients are enrolled, futility analyses will be presented to the DSMB by the unblinded statisticians based on conditional power estimates. Conditional power incorporates the observed results by treatment group thus far (and uses the originally assumed treatment effect for future data) to calculate the conditional probability of obtaining a significant result by the end of the trial. If conditional power, given the observed data and assuming the originally hypothesized treatment effect thereafter, is less than 10%, consideration should be given to stopping the trial.

7 Protection of Human Subjects & Other Ethical Considerations

7.1 Participating Clinical Sites and Local Review of Protocol and Informed Consent

This study will be conducted by major medical centers participating in the International Network of Strategic Initiatives in Global HIV Trials (INSIGHT). It is anticipated that potential participants will be recruited by the site investigators and/or that positive influenza laboratory testing will be used to enquire about potential enrollment. Information about this study will be disseminated to health care providers in these settings.

Prior to the initiation of the study at each clinical research site, the protocol, informed consent form and any participant information materials will be submitted to and approved by the site's Institutional Review Board (IRB) or Institutional Ethics Committee (EC). Likewise, any future amendments to the study protocol will be submitted and approved by each site's IRB or EC. After IRB/EC approval, sites must register for this study before screening potential participants, and must register for any protocol amendments. Protocol registration procedures are described in the *FLU-IVIG Protocol Instructions Manual*.

7.2 Ethical Conduct of the Study

The study will be conducted according to the Declaration of Helsinki in its current version; the requirements of Good Clinical Practice (GCP) as defined in Guidelines, EU Clinical Trials Directive (2001/20/EC), and EU GCP Directive (2005/28/EC); International Conference on Harmonization (ICH) Guidelines; Human Subject Protection and Data Protection Acts; the US Office for Human Research Protections (OHRP); or with the local law and regulation, whichever affords greater protection of human subjects.

7.3 Informed Consent of Study Participants

Informed consent must be obtained (see sample in Appendix A) prior to conducting any study-related procedures.

7.4 Confidentiality of Study Participants

The confidentiality of all study participants will be protected in accordance with GCP Guidelines and national regulations.

7.5 Remuneration of Study Participants

INSIGHT will provide funds to sites to permit compensation of enrolled study participants for the time and inconvenience associated with their study participation. The ceiling for this remuneration will be fixed and should be provided by the site to each participant on a pro-rated basis depending upon the number of study visits they successfully complete. However, it is anticipated that each participating site may have differing institutional policies or standards in regards to the types and amount of total compensation that can be offered to research participants and that the site IRB/EC will review and approve this compensation on a site-specific basis.

8 Other Important Documents and Policies

8.1 Reference Documents

Study procedures are described in detail in the *FLU-IVIG Protocol Instructions Manual.* Instructions for handling, storing, and shipping specimens are found in the *INSIGHT FLU-IVIG Laboratory Manual.* Procedures for the pharmacist are described in detail in the *FLU-IVIG Pharmacy Manual.*

8.2 Data Monitoring

Study data will be made available to site monitoring personnel. Monitoring may be performed by staff from INSIGHT International Coordinating Centers (ICC), by contractors of the primary funder, or by the Food and Drug Administration (FDA).

At a minimum, all items referenced in the protocol as being relevant to the research study will be recorded in the participant's research record in accordance with standard procedures.

8.3 Storage and Use of Specimens

Study participants consenting to this study consent to all study procedures, including collection of specimens. A participant may withdraw consent from the study at any time. If a participant requests that their specimens collected to date be destroyed, this request would be honored. Upon being informed that a participant has withdrawn consent for storage of specimens, the study database will be updated to indicate this, the specimen repository will be notified, and every effort will be made to have the specimens destroyed.

Stored respiratory specimens in this study will be used for RT-PCR testing for influenza and additional virological characterization, which may include but is not limited to subtype, antigenic and genetic analyses of the virus. The serum specimens collected at baseline and during follow-up will be used for measurement of hemagglutination inhibition (HAI) antibody titers. Future research using serum and plasma specimens may include, but is not limited to, the determination of biomarkers that could be associated with specific clinical outcomes.

Proposed research utilizing stored samples will be reviewed and approved by the Protocol team, the INSIGHT Scientific Steering Committee, and NIAID. Samples will not be sold to third parties or used directly to produce commercial products.

Further information regarding the use of stored specimens can be found in Appendix F.

8.4 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. The FDA requires study records to be retained for up to two years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be

maintained in compliance with IRB/EC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent required by federal, state, and local law.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator must provide written notification of such intent to the sponsor with the name of the person who will accept responsibility for the transferred records and/or their new location. NIAID must be notified in writing and written permission must be received by the site prior to destruction or relocation of research records.

8.5 Publications and Presentations

Publications and presentations related to data obtained from this study will adhere to the INSIGHT Publications and Presentations Policy on the INSIGHT website.

APPENDIX A: Sample Consent Form Documents

None of the changes to the FLU-IVIG protocol from Version 1.0 to Version 2.0 necessitated a change in the existing consent template. However, the protocol revision was seen as an opportunity to use the findings of the START Informed Consent substudy (as yet unpublished), that a more readable consent did not reduce comprehension of important consent information and was well-received by participants.

Along with the original sample informed consent (unchanged from Version 1.0), a simplified sample informed consent is also included in this version of the FLU-IVIG protocol. Readability statistics generated by Microsoft Word for the two versions are presented below. Both templates contain all of the required elements of consent according to ICH GCP.

Original consent		**Simplified consent**	
Counts		Counts	
Words	2,180	Words	2,386
Characters	9,833	Characters	10,503
Paragraphs	69	Paragraphs	140
Sentences	119	Sentences	162
Averages		Averages	
Sentences per paragraph	2.1	Sentences per paragraph	1.6
Words per sentence	17.4	Words per sentence	12.8
Characters per word	4.3	Characters per word	4.2
Readability		Readability	
Passive sentences	26%	Passive sentences	20%
Flesch Reading Ease	65.9	Flesch Reading Ease	75.0
Flesch-Kincaid Grade Level	8.3	Flesch-Kincaid Grade Level	5.9

At this time, the simplified consent template is not being translated into languages other than English. English-speaking sites may choose to use either one of these samples as the basis for their site-specific informed consent document, but should use the same consent for all participants. Should the simplified consent be translated in the future, any site may choose to use it in place of the standard consent.

APPENDIX A.1: Standard Sample Consent Form

Protocol Title:
Anti-Influenza Hyperimmune Intravenous Immunoglobulin Clinical Outcome Study (INSIGHT 006)

Sponsored by:
The University of Minnesota

A Multicenter Study of the
International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

Short Title of the Study: FLU-IVIG Study

CONSENT FOR PARTICIPATING IN AN NIH-FUNDED RESEARCH TRIAL

SITE INVESTIGATOR: _____ PHONE: _____

ALL SITE INSTRUCTION THAT IS INCLUDED IN A TEXT BOX SHOULD BE REMOVED FROM THE SITE'S INFORMED CONSENT FOR PARTICIPANTS

OHRP Requirements to be read by the sites:

PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB/EC REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB/EC WITH A COPY OF THIS SAMPLE LANGUAGE ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBs/ECs ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OR SUBSTANTIVE CHANGE OF INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENT MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB/EC, AND NOTED IN THE IRB/EC MINUTES. JUSTIFICATION AND IRB/EC APPROVAL OF SUCH CHANGES MUST BE FORWARDED TO THE INTERNATIONAL COORDINATING CENTER. SPONSOR-APPROVED CHANGES IN THE PROTOCOL MUST BE APPROVED BY THE LOCAL IRB/EC BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB/EC MAY OTHERWISE ADDITIONALLY REQUIRE.

We are asking you to join the INSIGHT 006 research study (the FLU-IVIG Study) because you are in the hospital with influenza (the "flu"). It is up to you whether or not you want to join this study; your participation is voluntary.

WHY ARE WE DOING THIS RESEARCH?

Influenza (the "flu") is a common illness that usually occurs in autumn and winter. The flu is usually mild, but can cause serious illness or death. There are not many good treatments available for severe flu. One possibility for a new treatment is to use

antibodies collected from people who have recovered from the flu or who have had a flu shot. Antibodies are made by the body to fight infection. They stick to the germ that causes the infection and make it easier for your immune system to find the germ and destroy it. These antibodies (also called intravenous immunoglobulin or "IVIG") may work to treat the flu. In this study we are using IVIG made by Emergent Biosolutions, a company very experienced in making this type of medication. IVIG is not currently approved for treating the flu. We are testing it in this study.

We are doing this study to find out if giving IVIG to people who are in the hospital for the flu will help them get better sooner, get out of the hospital sooner, and have fewer bad effects from the flu. We plan to enroll about 320 patients in different countries over one or more flu seasons. It is possible we might need more people to answer the study question, and, if so, we might enroll up to 470 patients.

HOW LONG WILL YOU BE IN THE STUDY?

You will be in the study for about 28 days.

WHAT WILL HAPPEN DURING THE RESEARCH?

Before you join this study:

- We will ask you questions about your medical history, medicines and treatments. We may get some of this information from looking at your chart.

- We will take 1-2 tablespoons (15-30 mL) of blood from a vein in your arm by using a needle. We will use this blood for normal medical tests to check your health.

If you are able to join this study, you will get the usual care for someone with the flu, which includes anti-flu medicines taken by mouth (like Tamiflu®) or by inhaling (like Relenza®). You will also get 1 of 2 study treatments decided by chance (like by flipping a coin). You will have an equal chance (50/50) of getting either treatment. The study treatments are:

1. IVIG mixed with normal saline (a salt solution). The amount of IVIG mixed in will depend on your weight.

2. Normal saline alone (no IVIG)

Both treatments are given one time intravenously (dripped through a tube attached to a needle in a vein in your arm). You will get about 2 1⁄4 cups (half a liter) of the study treatment. Neither you nor your doctor or nurse will know which of the 2 treatments you will receive. The treatment will be given over at least 2 hours. The antibodies from the IVIG will last for several weeks in your body.

At certain times during the study, we will draw about 1- 2 tablespoons (15-30 mL) of blood and send it to a central laboratory for tests. This will help us understand how high the level of antibodies gets within your blood. Neither you nor your doctor will receive the results of these tests.

We will see you while you are in the hospital. When you go home, we will give you a diary and ask you to record symptoms you have at home.

We will collect additional information or samples at the following times:

1. On the day of study enrollment, before you are given your study treatment:
   - We will draw 1-2 tablespoons (15-30 mL) of blood to be sent to a central laboratory.
   - We will take a sample from your nose and throat using a swab (like a Q-tip) to do tests that will tell us how much flu virus is in your body and what type of flu you have.
2. At 1 day after enrollment, we will draw 1-2 tablespoons (15-30 mL) of blood to be sent to a central laboratory.
3. For the 3 days after enrollment, we will check with you daily to see how you are feeling.
4. At 3 days after enrollment:
   - We will take another sample from your nose and throat using a swab (like a Q-tip) to do tests that will tell us how much flu virus is still in your body.
   - We will draw 1-2 tablespoons (15-30 mL) of blood, to be sent to a central laboratory.
5. At about 7 days after enrollment:
   - We will draw 3-4 tablespoons (45-60 mL) of blood. We will use about half of this blood for normal medical tests, to see how the study treatment is affecting you.
   - We will send the rest of this blood sample to a central laboratory.
   - We will ask you questions about how you are feeling.
6. At about 14 days after enrollment, we will check with you to find out how you are feeling. This will probably be done by telephone.
7. At about 28 days after enrollment, we will check with you to find out how you are feeling. This will probably be done by telephone. This will be the last study visit.

We may need to get some of the study information from your medical record. By signing this consent you also agree to let us get information that is related to this study from your medical record.

WHAT HAPPENS TO THE SAMPLES?

The swab samples from your nose and throat will be sent to a central laboratory in the United States to test the amount and type of flu virus in your body. Neither you nor your doctor will get the results of these tests.

Some of the blood samples will be sent to a local laboratory for normal medical tests to check your health and see how the treatment is affecting you. Your doctor will get the results of these tests and may share these results with you. Other blood samples will be sent to the same central laboratory in the United States as the swab samples. These blood samples will be tested to see how many flu antibodies are in your blood – how your immune system responded to your illness. Neither you nor your doctor will get the results of these tests.

Part of the samples will be stored at the central laboratory and may be used in the future by members of the study team to answer other questions about the flu. The samples will not be used for commercial use, and no human genetic testing will be done. No additional tests are planned at this time. There is no time limit on how long your samples will be stored.

WHAT ARE THE RISKS AND/OR DISCOMFORTS OF BEING IN THIS STUDY?

There are some possible side effects of getting IVIG. Some of the more common side effects are fever, rash, hives, or headache.

Serious and potentially fatal side effects are rare. These include serious allergic reactions, kidney problems, a lung injury that makes it hard to breathe, a higher risk of blood clots, meningitis (a type of brain swelling), and a condition called hemolysis, where red blood cells open up and spill their contents into surrounding fluid (plasma).

Because IVIG is made from the blood of other people, it is possible that the blood could contain a virus. Although all blood that is used for making the IVIG is carefully checked for infections and is treated to kill any known viruses, we cannot be absolutely sure that using IVIG will not give you other types of infections.

You should wait three months or more after having the study treatment before you get live attenuated (weakened) virus vaccines like those for measles, rubella, mumps and varicella (chickenpox or shingles). This is because the IVIG may temporarily make your body unable to respond to the vaccines as well as you would like.

The risks of having blood taken or having an intravenous line put in your arm include short-lasting pain, bleeding, bruising, lightheadedness, fainting and, rarely, infection or a blood clot where the needle enters your body. Some people have mild discomfort or gag when samples are taken from their throat or nose. Even if you decide not to be in this study, you will likely have these sorts of tests done as part of your usual medical care for the flu.

An independent Data and Safety Monitoring Board (DSMB) will look at results from the study at least every six months. The DSMB is made up of doctors and other people with a good understanding of influenza and of studies like this one. They will help to try to keep the study safe for all participants.

WHAT ARE THE BENEFITS OF BEING IN THIS STUDY?

We do not know whether being in the study will help you. About half of the people in this study will actually get IVIG. We think that adding IVIG to the usual anti-flu medicines may help you get over your flu faster, but we do not know that for sure. What we learn from this study will help decide if IVIG should be recommended for treating flu in the future. About half the people in the study will get a salt water solution and will not get IVIG, and we do not expect any benefit at all for those people. The chance of getting IVIG or getting salt water solution is random, like flipping a coin.

WHAT ARE THE COSTS TO YOU?

The study treatment will be provided at no cost to you. We will provide all clinical services, lab work, and other tests that are part of this study. You, your insurance company, or some other third-party payer must pay for all other medicines and any required hospital stay.

WHAT IF YOU ARE INJURED AS PART OF THIS STUDY?

If you are injured because of being in this study, *[insert the name of the clinic]* will give you immediate necessary treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. The study cannot pay you or pay for any care for study-related injuries or for your illness.

WHAT ABOUT PREGNANCY AND BREASTFEEDING?

Women who are pregnant or breastfeeding cannot join this study. If you are a woman who can get pregnant, you will have a blood or urine test to see if you are pregnant before you can join the study. If you are in this study, you must agree to either not have sex that could make you pregnant while you are in the study, or to use at least one type of birth control, either a barrier type (condom, diaphragm, IUD, etc.) or a hormonal type (birth control pills, Depo-Provera, etc.).

WHAT CHOICES DO YOU HAVE OTHER THAN BEING IN THIS STUDY?

You do not have to join this research study if you do not want to. If you join, you may decide to quit at any time. If you choose not to join or to quit, it will not change your regular medical care. If any new information becomes available that might change your decision about joining or staying in the study, we will tell you about it right away.

WHAT ARE ALTERNATIVE TREATMENTS?

If you do not want to be in this study, you can get the usual medicines to treat the flu. However, you cannot get the experimental IVIG treatment.

HOW IS YOUR PRIVACY PROTECTED?

We will protect the privacy of your medical information as much as legally possible, and release your records only with your written permission. We will label your study records with a code number and three letters, and you will not be identified in any publications about this research. However, your records may be seen by:

- People in the U.S. government agencies that fund or oversee this research, for example, the U.S. National Institutes of Health (NIH) and the Food and Drug Administration (FDA).
- Study monitors who make sure the study is being conducted correctly.
- Independent groups such as institutional review boards (IRBs) or ethics committees (ECs) that make sure the study is ethical (fair).

COMPENSATION

Compensation will be offered for your time and inconvenience participating in the study. *[additional details to be completed by site]*

WHO CAN I TALK TO ABOUT THIS STUDY?

For questions about this study, or about the storage or use of your samples, and in case of any research-related injury, contact:

• *[name of the investigator or other study staff]* • *[telephone number of above]*

For questions about your rights as a research participant contact:
• *[name or title of person on the ethics committee (Institutional Review Board, IRB) or other organization appropriate for the site]*
• *[telephone number of above]*

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE INSIGHT 006 STUDY

If you have read the consent (or if you have had it explained to you) and understand the information, and you voluntarily agree to join this study, please sign your name below.

I agree to participation in the INSIGHT 006 study (FLU-IVIG Efficacy) as described in this consent document.

_____
Participant's name (typed or printed)

_____ _____
Signature of participant or legal representative Date

_____
*Witness's name (typed or printed)

_____ _____
Witness's signature Date

_____
Name of staff member conducting consent process (typed or printed)

_____ _____
Staff member's signature Date

***A witness to the participant's signature is strongly encouraged.**

NOTE: This consent form, with the original signatures, MUST be retained on file by the Investigator of Record. A copy must be given to the participant. A copy should be placed in the participant's medical record, if applicable.

APPENDIX A.2: Simplified Sample Consent Form

Study Title: Flu Treatment Study (FLU-IVIG)

Sponsored by:
The University of Minnesota

A Multicenter Study of the
International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

Full Title of the Study: Anti-Influenza Hyperimmune Intravenous Immunoglobulin Clinical Outcome Study (INSIGHT 006) – Version 2.0, 31-May-2016

CONSENT FOR PARTICIPATING IN AN NIH-FUNDED RESEARCH STUDY

SITE INVESTIGATOR: _____ PHONE: _____

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INTRODUCTION

This information is about a study for treating the flu (influenza).

WHY HAVE I BEEN GIVEN THIS INFORMATION?

You have been given this information in case you want to join the study.

You are being asked to join because you are in the hospital with the flu.

WHAT IS INVOLVED IF I WANT TO JOIN?

Before you can decide whether or not to take part, you will need to know:

- Why the study is being done.
- What is involved.
- Whether there are advantages to your health.
- Whether there are any risks.

You can also talk to your doctor or other health provider about the study. You can also discuss it with your family and friends.

If you have questions, please ask your doctor or other health worker to answer these until you are happy with the answers,

DO I HAVE TO JOIN THE STUDY?

No. Taking part is voluntary. This means:

- Whether or not you decide to take part is your choice.
- If you join the study and then change your mind, you can stop later.
- If you decide not to take part, it will not affect your health care in the future.

WHAT HAPPENS IF I DECIDE TO TAKE PART?

If you agree to take part, you will be asked to sign this consent form.

You will be given a copy of the signed consent form to keep.

If someone is representing you, they will be asked to sign this form.

WHY ARE WE DOING THIS STUDY?

The flu is a common illness that usually occurs in fall (autumn) and winter. For most people the flu is usually mild. In some cases it can cause serious illness or death.

There are very few treatments for severe flu.

One possible new treatment is to use immune responses (called antibodies).

This study uses antibodies taken from people who had the flu and got better, or who had a good response to a flu vaccine.

Antibodies are made by the body to fight infection. They stick to the flu virus that causes the infection. This makes it easier for your immune system to find the flu virus and kill it. Giving people these antibodies may help to treat the flu.

The antibodies used are called intravenous immunoglobulin or IVIG. This is pronounced "I.V.I.G."

This study is to find out if IVIG helps people who are in the hospital for the flu.

We want to see whether it will help in three ways.

1. To help get better sooner.

2. To be able to get out of the hospital sooner

3. To have fewer bad effects from the flu.

In this study we are using IVIG made by Emergent BioSolutions. Emergent is very experienced in making IVIG. IVIG is not approved for treating the flu. We are testing it in this study.

HOW MANY PEOPLE WILL TAKE PART?

The study will enroll about 320 participants.

This will include people in different countries over several flu seasons.

If more people are needed, the study might enroll up to 470 people.

HOW LONG WILL YOU BE IN THE STUDY?

You will be in the study for about 28 days.

After you leave the hospital, you will be contacted by telephone on days 14 and 28 to see how you are feeling.

HOW WILL THE STUDY WORK?

Before you can join this study, we want to make sure it will be safe for you to do so:

- We will check your medical history and treatments. We may get this from looking at your medical records, or may ask you questions.

- We will also take 1-2 tablespoons (15-30 mL) of blood. We will take this blood from a vein in your arm using a needle. We will use this blood for routine medical tests to check your health.

If you are able to join this study, you will get the all usual care for someone with the flu. This includes oral medicines (like Tamiflu®) or inhaled medicine (that you breath in) (like Relenza®).

Besides your usual care, you will also be randomized to one of two study groups. The treatment you get will be decided by chance, like by flipping a coin. You will have an equal chance (50/50) of getting either treatment.

This is called a double-blind study. Neither you nor the doctors and nurses will know which group you are in.

The only person to know which treatment you get will be the pharmacist who makes up your treatment. They are not allowed to tell anyone this, even the researchers.

The study groups are:

1. To have a single infusion of IVIG mixed with a salt solution. The amount of IVIG mixed in will depend on your weight. This is the experimental treatment.

2. To have a single infusion of a salt solution (with no IVIG). This is an inactive solution or placebo, and is the comparison group.

No matter which treatment you get, you will only get it once.

The infusion is given by a drip through a tube attached to a needle in your arm. This is called intravenously (IV), The infusion is about 2 1⁄4 cups (half a liter).

You will get the infusion the same day you join the study, within a few hours after you join. The infusion will take at least two hours.

We will see you while you are in the hospital. When you go home, we will give you a diary and ask you to record symptoms you have at home.

WHAT INFORMATION IS COLLECTED AND AT WHAT TIMES?

The following information will be collected at these times:

Day 0 (the day you join the study)	Day 1	Day 3	Day 7
• Infusion of study treatment • Sample from your nose or throat using a swab (like a Q-tip) • Blood for future research	• Blood for future research • We will check how you are feeling every day through Day 3	• How you are feeling • Sample from your nose or throat using a swab (like a Q-tip) • Blood for future research	• How you are feeling • Blood tests to check your health • Blood for future research

At about Day 14 and Day 28 after you join, we will check with you to find out how you are feeling. This will probably be done by telephone. Day 28 is the last study visit.

We may need to get some information from your medical record. By signing this consent you also agree to let us get information for this study from your medical record.

WHAT HAPPENS TO THE BLOOD AND SWAB SAMPLES?

Some of the blood samples will be sent to the local laboratory for normal medical tests to check your health. Your doctor will get the results of these tests and may tell you the results.

The swab samples from your nose or throat will be sent to a central laboratory in the United States. This is to measure how much flu virus you have. You and your doctor will **not** get the results of these tests.

Other blood samples will be sent to the same central laboratory in the United States as the swab samples. This is to measure how many flu antibodies are in your blood. This tells us how your immune system responded to your flu. You and your doctor will **not** get the results of these tests.

Any blood and swab samples that are leftover will be stored at the central laboratory. These might be used in the future to answer other questions about the flu.

We do not know yet what this future research will involve. You and your doctor will **not** get any results from these tests. These samples will not be sold or used for commercial research. We will not test your DNA (your genes). We do not have a time limit for how long we keep your samples.

WHAT ARE THE RISKS AND/OR DISCOMFORTS OF BEING IN THIS STUDY?

All treatments can cause side effects. You may have some side effects from IVIG. These are some common side effects that are not usually serious:

- Fever
- Rash
- Hives
- Headache.

It is rare for IVIG to cause serious side effects, but it can happen. These are some of the serious effects that can happen:

- Serious allergic reactions
- Kidney problems
- A lung injury that makes it hard to breathe
- Blood clots
- A type of brain swelling called meningitis
- A condition called hemolysis, where red blood cells open up and spill their contents into surrounding fluid.

IVIG is made from the blood of other people. All blood that is used for making IVIG is carefully checked and is treated to kill any known viruses. However, we cannot be totally sure that you will not get other types of infections from IVIG.

IVIG may temporarily make you not able to respond to vaccines as well as usual. You should wait at least three months after having the study treatment before you get live attenuated (weakened) virus vaccines such as measles, mumps, rubella, and varicella (chickenpox or shingles). Measles, mumps, and rubella vaccines are sometimes given in one shot called “MMR.”

When you have blood taken or have a tube put in your arm for the study treatment, you might have short-lasting pain or bleeding. You might have a bruise or a small wound. You could get lightheaded or faint. You could get an infection or a blood clot where the needle enters your body, but this is very rare.

You might gag or feel uncomfortable when the swab is put in your nose or throat.

You will likely have these sorts of tests done as part of your care for the flu, even if you decide not to be in this study.

WHAT ARE THE BENEFITS OF BEING IN THIS STUDY?

We do not know if being in the study will help you.

About half of the people in this study will actually get IVIG. If you get IVIG, we think that adding it to the usual anti-flu medicines may help you get over your flu faster, but we do not know for sure. This is what we are trying to find out in this study.

About half the people in the study will get a salt water solution and will not get IVIG. If you do not get IVIG, we do not expect you to have any benefit.

What we learn from this study will help decide if IVIG should be recommended for treating flu in the future.

WHAT ARE THE COSTS TO YOU?

We will give you the study treatment at no cost. We will pay for all clinic visits, lab work, and other tests that are part of this study.

THE NEXT PARAGRAPH IS FOR UNITED STATES SITES ONLY. SITES IN OTHER COUNTRIES SHOULD DELETE THE NEXT PARAGRAPH.

You, your insurance company, or some other third-party payer must pay for all other medicines and hospital costs.

SITES OUTSIDE THE UNITED STATES: Please replace the paragraph above with language appropriate for your location.

WHAT ABOUT PREGNANCY AND BREASTFEEDING?

Women who are pregnant or breastfeeding cannot join this study.

If you are a woman of child bearing potential, we will test to see if you are pregnant before you can join the study.

If you join this study, you must agree to either not have sex that could make you pregnant while you are in the study, or to use at least one type of birth control, either a barrier type (condom, diaphragm, IUD, etc.) or a hormonal type (birth control pills, Depo-Provera, etc.).

WHAT IF NEW INFORMATION BECOMES AVAILABLE?

If we have any new information that might change whether you want to join or stay in the study, we will tell you right away.

WHAT CHOICES DO YOU HAVE OTHER THAN BEING IN THIS STUDY?

You do not have to join this research study if you do not want to.

If you join, you may stop at any time. If you choose not to join or to stop, your regular medical care will not change.

WHAT ARE ALTERNATIVE TREATMENTS?

If you do not want to be in this study, you will still get the usual medicines and other care to treat the flu. However, you cannot get the IVIG treatment, because it is experimental.

WHAT IF YOU ARE HURT AS PART OF THIS STUDY?

If you are hurt because of being in this study, *[insert the name of the clinic]* will treat your injury right away. You or your insurance will have to pay for this treatment. The study cannot pay you or pay for any care for study-related injuries or for your illness.

If the above is not true for your site, i.e., if trial insurance covers such cost, please replace the sentence with appropriate language.

HOW IS YOUR PRIVACY PROTECTED?

We will take every reasonable step to keep your health information private and to prevent misuse of it.

Your data (information) and samples (blood and swab) will not be identified by name, or in any other way, in anything published about this study.

You will be identified only by a code. We will not release personal information from your records without your written permission.

[The following paragraph is for sites outside the US only]
We will do everything we can to keep your personal information private, but we cannot guarantee that nobody will get it. We may have to release your personal information if required by law.

[The following paragraph is for all sites]
The following people may see your medical and research information:

- the *[insert the name of the site]* ethics committee (institutional review board, IRB);
- the research staff and monitors and their designees.

They are committed to protect your privacy.

As the research staff at *[insert the name of the site]*, we are required to make sure that people not involved with this study cannot see your research and medical information while collecting personal information about you.

We will keep your files in a locked cabinet in a safe place and will handle your personal information very carefully. This will also help to protect your privacy.

WILL YOU BE PAID TO BE IN THE STUDY?

We will compensate you for your time and inconvenience participating in the study. *[specific details to be completed by site]*

WHAT IF YOU HAVE PROBLEMS OR QUESTIONS?

If you ever have questions about this study, or about the storage or use of your samples, or if you are hurt by being in the study, contact:

• *[name of the investigator or other study staff]* • *[telephone number of above]*

If you have questions about your rights as a research participant, you can call:
• *[name or title of person on the ethics committee (Institutional Review Board, IRB) or other organization appropriate for the site]*
• *[telephone number of above]*

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN THE INSIGHT 006 STUDY (FLU-IVIG Efficacy)

If you have read the consent (or if you have had it explained to you), you are satisfied that you understand the information, and you want to join this study, please sign your name below.

_____	_____	_____
Participant's name (typed or printed)	Participant's signature	Date

OR

_____	_____	_____
Surrogate/representative's name (typed or printed)	Surrogate/representative's signature	Date

_____

*Witness's name (typed or printed)

_____ _____

Witness's signature Date

_____

Name of staff member conducting consent process (typed or printed)

_____ _____

Staff member's signature Date

***A witness to the participant's (or surrogate/representative, if applicable) signature is strongly encouraged.**

NOTE: This consent form, with the original signatures, MUST be retained on file by the Investigator of Record. A copy must be given to the participant. A copy should be placed in the participant's medical record, if applicable.

Appendix B: Time and Events Schedule

Screening and Baseline		
	Day -2 to 0	**Day 0**
ELIGIBILITY AND SCREENING		
Informed consent	X	
Demographics, medical history	X	
Influenza testing	X	
Pregnancy test, if child-bearing potential	X	
CBC, Chemistry panel, PTT/PT/INR[a]	X	
NEW score	X	
DAY OF RANDOMIZATION		
Assessment of targeted symptoms		X
NEW score[b]		X
Randomize participant		X
Serum & plasma for storage & serology[c]		X
NP swab for virus isolation		X
IVIG/placebo infusion		X

	Day 1	**Day 2[d]**	**Day 3**	**Day 7** +1 day	**Day 14[d]** ±2 days	**Day 28[d]** +7 days
STUDY PROCEDURES						
NEW score[e]	X	X	X			
Assessment of targeted symptoms[f]			X	X		
Clinical data	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
LOCAL LAB						
CBC, Chemistry panel[a]				X		
CENTRAL LAB						
NP swab for virus isolation			X			
Serum & plasma for storage and serology[c]	X		X	X		

[a] CBC includes white cell count with differential (neutrophil, lymphocyte, eosinophil percentages), hemoglobin, hematocrit, and platelets. Chemistry panel includes sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT/GPT, AST/GOT, total bilirubin.
[b] NEW score must be repeated on day 0 if the score used for screening was from a previous day. The NEW score at screening must be ≥ 2.
[c] Sufficient for 4 1-mL aliquots of serum and 4 1-mL aliquots of plasma
[d] May be assessed via telephone, if not hospitalized.
[e] Assessed twice daily, at 8:00 AM and 4:00 PM (±2 hours), while hospitalized.
[f] Participants are given a diary at hospital discharge to use for this assessment, and for recording resolution of flu symptoms and return to normal activities.

Appendix C: INSIGHT 006: FLU-IVIG Protocol Team

To oversee the implementation of this randomized clinical trial, membership on the broader protocol team will include:

- Protocol co-chairs
- NIAID representatives
- INSIGHT International Coordinating Center representatives
- INSIGHT medical monitor
- Collaborating laboratory representatives
- Site investigators
- INSIGHT infrastructure representatives
- Study biostatisticians
- Community representatives

Appendix D: Reference on INSIGHT Website

The INSIGHT website (**www.insight-trials.org**) will maintain updated links to the following documents referenced in the FLU-IVIG protocol and to other information pertinent to the study:

- The *FLU-IVIG Protocol Instructions Manual*
- The *FLU-IVIG Laboratory Manual*
- The *FLU-IVIG Pharmacy Manual*
- Investigator's Brochure for IVIG
- The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (or "DAIDS AE Grading Table")
- INSIGHT Publications and Presentations Policy

Appendix E: List of Acronyms

AE	Adverse Event
BMT	Bone marrow transplant
CBC	Complete blood count
CFR	Code of Federal Regulations (U.S.)
CI	Confidence interval
C_{MAX}	Maximum concentration
CMV	Cytomegalovirus
CRF	Case Report Form
CSO	Clinical Safety Office
DHHS	Department of Health and Human Services (U.S.)
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECMO	Extracorporeal membrane oxygenation
EU	European Union
FDA	Food and Drug Administration (U.S.)
g	grams
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
H-IVIG	Hyperimmune intravenous immunoglobulin
HAI	Hemagglutination inhibition
HAV, HBV, HCV	Hepatitis A, B, C virus
HBsAg	Hepatitis B surface antigen
IB	Investigators Brochure
ICU	Intensive care unit
IEC	Institutional Ethics Committee
INR	International normalized ratio
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IRB	Institutional Review Board
IVIG	Intravenous immunoglobulin
mL	Milliliter
mm	Millimeter
NAT	Nucleic acid testing
NIAID	National Institute of Allergy and Infectious Diseases, NIH (U.S.)
NIH	National Institutes of Health (U.S.)
NEW	National Early Warning
NEWS	National Early Warning Score
NP	Nasopharyngeal
OHRP	Office for Human Research Protections (U.S.)
PID	Participant Identification Number
PIM	Protocol Instructions Manual
PK	Pharmacokinetics
PT	Prothrombin time

PTT	Partial thromboplastin time
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcriptase-polymerase-chain-reaction
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SDMC	Statistical and Data Management Center
SOC	Standard of care
SSC	Scientific Steering Committee (INSIGHT)
SUSAR	Suspected Unexpected Serious Adverse Reactions
TRALI	Transfusion-related acute lung injury
UP	Unanticipated Problem
U.S.	United States of America
VIG	Vaccinia immune globulin
Vz	Volume distribution
WBC	White Blood Cell Count
WHO	World Health Organization

APPENDIX F: Policies for Specimen Storage and Use

Storage and Use of Specimens in INSIGHT Protocol 006: FLU-IVIG (02 September 2014)

This document outlines the procedures for storage, acquisition and utilization of stored samples collected in the FLU-IVIG Study.

1. Laboratories and Repository

All participant blood and respiratory specimens collected through this INSIGHT study are sent along with specimens for other INSIGHT studies to Advanced BioMedical Laboratories (ABML) L.L.C., P.O. Box 2289/1605 Industrial Hwy, Cinnaminson, NJ 08077-2289, United States for cataloguing. From there, the specimens from the FLU-IVIG Study will be sent to Leidos Biomedical Research, Inc. 1066 Boyles Street, Second Floor, Room 201, Frederick, MD 21702, United States, for RT-PCR testing and long-term storage. The results of all testing of the stored specimens will be transferred to the Statistical and Data Management Center (SDMC) for analysis and will become part of the FLU-IVIG Study database.

2. Acquisition of specimens

Study participants must have consented to INSIGHT 006 prior to any study procedures, including collection of specimens. A participant may withdraw consent from the study at any time. If a participant requests that their specimens collected to date be destroyed, this request would be honored. Upon being informed that a participant has withdrawn consent for storage of specimens, the SDMC database will be updated to indicate this, the specimen repository will be notified, and every effort will be made to have the specimens destroyed. In no case will these specimens be selected for use in analysis after consent has been withdrawn. If samples have already been tested prior to the revocation of consent, the results of the testing remain part of the research.

Participant privacy is protected through labeling specimens with unique codes. Specimens that are released to collaborators for approved research are identified only by these unique codes. Personal identifying information is maintained only at the participant's clinical site and is never provided to the SDMC, repository, or collaborating researchers.

3. Utilization of stored samples

a. Planned uses for stored blood and respiratory specimens in INSIGHT 006

Respiratory specimens in INSIGHT 006 will be used for RT-PCR testing for influenza. The serum specimens collected at baseline and during follow-up will be used for

measurement of hemagglutination inhibition (HAI) antibody titers. Future use of stored specimens may include, but is not limited to, antigenic and genetic analyses of the virus and determination of biomarkers that could be associated with specific clinical outcomes.

Samples will not be sold to third parties or used directly to produce commercial products.

b. Approval of proposed research using specimens

1) Scientific approval

Specimens are requested by preparing a Research Proposal available on the INSIGHT website, www.insight-trials.org, under "New Science" on the home page. The INSIGHT Scientific Steering Committee (SSC) reviews all research proposals for use of the stored specimens. The evaluation of every request entails consideration of its scientific merit in the context of other investigators' requests and the limited availability of specimens. The INSIGHT 006 Protocol Team will assist the SSC with the scientific evaluation of specimen proposals. At the discretion of the SSC, additional review of a given proposal may also be solicited from an INSIGHT Interest Group whose field of interest is of most relevance to that request.

2) Ethical approval

An application will be submitted to the University of Minnesota Health and Medical/Biological Institutional Review Board (U of M IRB) requesting a Category 4 IRB determination that the specific uses of specimens collected in INSIGHT 006 are exempt from IRB Committee review for a period of five years. This determination is usually granted if:

- All of the specimens were obtained from participants who consented to the specimen collection using a local IRB/EC approved informed consent, **and**
- All specimens are de-identified and confidentiality is assured.

If local IRBs request notification of proposals that have been approved to move forward, this will be provided to them. If they do not approve the research using stored samples from patients under their jurisdiction, they are to notify the INSIGHT Executive Committee (EC). Upon receiving this notification, the SDMC will note in the database that these samples are not to be used in the research proposal.

c. Publication of research using specimens

1) Collaborating investigators agree to the Publications & Presentations Policy on the INSIGHT website (www.insight-trials.org) > Publications & Presentations> Resources> "Publications & Presentations Policy".

1. The INSIGHT funders are acknowledged in all such publications and presentations.
2. Abstracts and manuscripts must be submitted to the INSIGHT 006 Protocol Team and the INSIGHT SSC for review and approval prior to submission to a

conference or journal. This will ensure that safety concerns or policy implications can be addressed and that all parties involved are appropriately recognized.

Summary

The stored specimens in INSIGHT 006 (FLU-IVIG) are a valuable resource for better characterizing predictors of outcomes for individuals with influenza infections. The availability of the repository may facilitate the discovery and validation of new biomarkers that may correlate with specific disease outcomes. These stored specimens will be made available to researchers with excellent research ideas so that the knowledge gained from the data and specimens provided by the participants can be maximized.

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