



# **Duke University Hospital Investigational Drug Service**

## **Dispensing Solutions**

Sharon Ellison, Pharm.D.  
February 6, 2006  
CTQA Lunch & Learn

# Investigational Drug Service Personnel

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Sharon Ellison, Pharm.D.

Greg Westby, R.Ph.

Malphus Stroud, C.Ph.T.

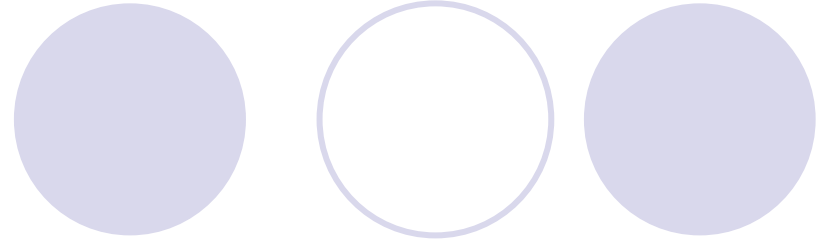
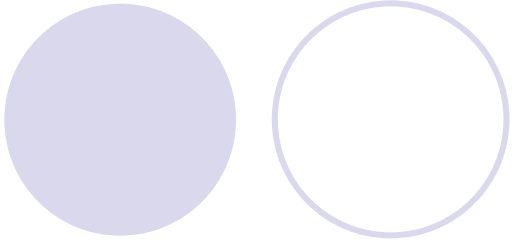
Richard Smith, C. Ph. T., CTA 1

Beth McLendon-Arvik, Pharm.D.

# Objectives

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- I. Provide an overview of the IDS Pharmacy
- II. Discuss medication safety and regulatory issues as it relates to clinical trials in the hospital setting
- III. Learn how IDS can help you with your studies



# 1. OVERVIEW OF IDS

# Trial Experience and History

## IDS Volumes

<u>Year</u>	<u>Concurrent Studies</u>
1985	start of IDS
1990	50
1994	106
1998	150
2002	170
2006	208!

# Recent Stats



- 208 protocols currently
- Mix of “active” and “pending”
- Received over 75 new protocols in 2005
- 45+ began enrolling in 2005
  
- The Broader picture:  
Approximately 700 drug studies going on here at Duke

# Other Pharmacies Involved in Research at Duke

- Investigational Cancer Service/“Oncology IDS”
  - Ashley Morris-Engemann, Pharm.D. and Cheryl Morgan, Clinical Trials Specialist
- HIV / AIDS Clinical Trials – Infectious Disease Clinic 2J
  - Ken Shipp, R.Ph.
- CHC Clinic Pharmacy – Outpatient Pediatric Studies
  - Christina Johnson, Pharm.D.

# IDS Experience



- Types of Studies

- Blinded
- Open-Label
- Treatment IND & Compassionate Use
- Pediatric, Adult, Inpatient, Ambulatory

- Research status of drugs

- IND 50%
- IND/Phase IV 36%
- Phase IV 14%

# IDS Site Information

- Secured-Controlled-Monitored Location
  - Duke South, Room 0101-B, Yellow Zone
- Facilities (monitored and alarmed)
  - 800 square feet office/storage space
  - Class I and II LF Hoods
  - Biologic isolation chamber
- Service Hours
  - On-site staff from 8 am to 4:30 pm M – F
  - 24/7 On – call

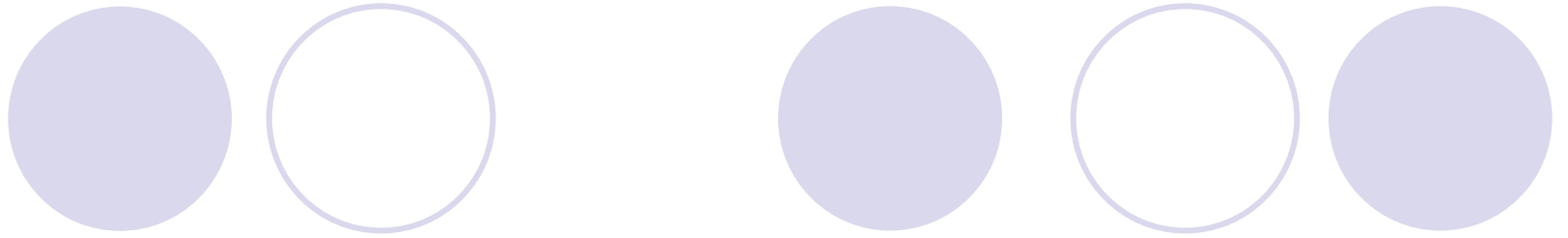
# IDS – IRB Relationship



- Membership on IRB's
  - 13 Pharmacy Members Currently
    - Covering 94 meetings/year
- Informational support to staff and chairs
- Student and resident attendance at IRB
- Develop protocol preparation checklists:
  - Drug nomenclature standards for consent forms
  - Safe medication practices
  - Eliminate unsafe abbreviations
  - Pharmacy review for inpatient studies

# Academic and Clinical Activities

- **Teaching** – Doctor of Pharmacy students
- **Precepting** – Post-doctoral residents/fellows
- **Research** – Advisors & retrospective study
- **Presentation** – National & State
- **Patient Care** – Ambulatory & Inpatient



## **2. MEDICATION SAFETY & REGULATORY ISSUES**

# Compliance

A decorative graphic at the top of the slide consists of two overlapping circles on the left and three separate circles on the right. The circles are light purple, with the leftmost and rightmost ones being solid and the middle one being an outline.

- JCAHO
- FDA
- NIH
- USP 797
- NC Board of Pharmacy
- Duke University Hospital Policy

# IDS Standards



- JCAHO

- **Standard MM.7.40**

- Investigational medicines are safely stored, controlled, administered and destroyed*

- Elements of performance (new): When the hospital “...operates a pharmacy, procedures specify the pharmacy controls the storage, dispensing, labeling, and distribution of the investigational medications.”

# IDS Standards



- FDA & NIH

- Follow GCP and GMP guidelines
- Maintain confidentiality
- Compounding standards
- Storage/Security standards
- Documentation standards

# IDS Standards



- USP/FDA (Enforceable Administrative Code)
  - Chapter 797 Standards – Effective July 1, 2004
    - Sterile preparations
    - Applies to all practitioners in all practice sites
    - Establishes minimum standard for process control, quality control, responsibilities of personnel, environmental controls, expiration times and more...

# IDS Standards



- NC Board of Pharmacy (Administrative Code)
  - Dispensing
    - Prepare, package, label (including refills and unit dose)
  - Labeling
    - Act of preparing and affixing label to container
  - Child-resistant packaging
    - Unit dose is not necessarily child-resistant

# NCBOP – Pharmacy Laws of NC

- **90-85.3.Definitions (f):** "Dispense" means preparing and packaging a prescription drug or device in a container and labeling the container with information required by State and federal law. Filling or refilling drug containers with prescription drugs for subsequent use by a patient is "dispensing." Providing quantities of unit dose prescription drugs for subsequent administration is "dispensing."

# Duke University Hospital

## Policies and Procedures

- Investigational drugs administered to patients by Patient Care Services nurses are dispensed from the Department of Pharmacy
- **Verbal** orders may not be given for:
  - Cancer chemotherapeutic agents
  - ***Investigational drugs***
  - Systemic thrombolytic agents. NOTE: **Verbal** orders may be given for alteplase (tPA) for the purpose of declotting a catheter.
  - Initial dose of insulin. NOTE: Preprinted insulin order sheet must be used for initial insulin orders

# New IRB Submission Page

- Is an investigational drug or device being used in this study?
- IND Number; holder of the IND
- If you are using an investigational drug in this study, are you using the Investigational Drug Service (IDS) at Duke?
- “Please be aware that inpatient administration of an investigational drug requires the use of the Duke IDS, as per Department of Pharmacy policy”

# Safe Medication Practices: Revised Prescribing Guidelines



- Approved by Medical Staff leadership and the Pharmacy & Therapeutics Committee in 2003
  - Defines minimum elements for a complete medication order
  - Eliminates usage of unsafe abbreviations



# Complete Medication Order

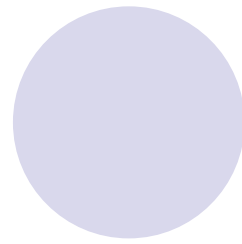
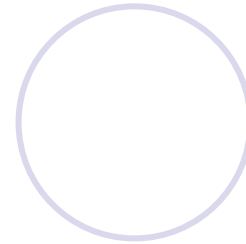
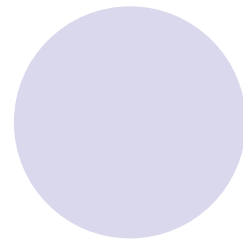
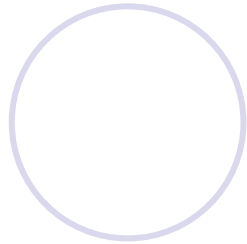
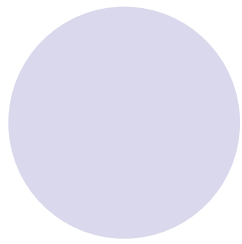
- Name and History Number
- Name of the medication
- Dose with units of measure
- Administration route
- Time and frequency of administration
- Titrated orders must be defined with desired effect
- “Range orders” (e.g. 1-2 tabs or 25-50 mg) eliminated wherever possible

# Unsafe/Unauthorized Abbreviations

<b>Do Not Use:</b>	<b>Instead Use:</b>
μ	mcg or microgram
U	unit
2.0 mg	2 mg
.25 mg	0.25 mg
M <sub>4</sub> SO <sub>4</sub> or MS	morphine
MgSO <sub>4</sub>	magnesium sulfate



### 3. HOW WE CAN HELP YOU -and how you can help us : )



# What Can We Do For You?

## Relationship and role to Pharmacy Services

- Consolidate activities and skills
  - Design → Implementation → Closeout
- Integrate research into patient care activities
- Comply with laws and standards
- Coordinate production & packaging function
- Educate staff on specifics of research

# IDS Operations



- Protocol Specific Services

- Online pharmacy procedures
- Online drug data sheets <http://pharmacy.mc.duke.edu>
- Randomization, storage/security, accountability, blinding, preparation/compounding, patient counseling, staff education
- Audits (FDA, CRO, Sponsor)
- Records management

# Pharmacy Memoranda

## MEMORANDUM

TO: SPA Pharmacy, Night Shift Pharmacy, Satellite Pharmacies, and IDS Personnel

FROM: Christine Szpak, UNC Pharm.D. Candidate

Sharon L. Ellison, Pharm.D. ID#: 970-3394  
Investigational Drug Service

DATE: January 26, 2006

RE: **A Randomised, Double-Blind, Placebo-Controlled, Multi-Centre, Parallel Groups, Confirmatory Efficacy and Safety Trial of Activated Recombinant Factor VII (NovoSeven®) in Acute Intracerebral Haemorrhage**

## STUDY PERSONNEL

*Principal Investigator:* Carmelo Graffagnino, MD ID# 970-3079  
*Study Coordinator:* Joanna Stoner, RN ID# 970-5903

*Study Sponsor:* Novo Nordisk A/S

## STUDY RATIONALE (synopsis from the study protocol)

Intracerebral Hemorrhage (ICH) is the most common type of nontraumatic intracranial hemorrhage and a major variety of stroke with a very poor prognosis. Currently, there is no specific therapy for ICH, only symptomatic treatment. At pharmacological doses, it is thought that rFVIIa may bind independently of tissue factor to activated platelets and locally initiate thrombin generation, which is important for the formation of the initial hemostatic plug. A previous trial showed that rFVIIa given within four hours of ICH onset reduced subsequent hemorrhage growth and improved clinical outcome. The rationale for the current study is to confirm the efficacy and safety results from the previous study of the 80 mcg rFVIIa/kg and at the same time, evaluate a low dose of 20 mcg rFVIIa/kg compared to placebo.

## STUDY OBJECTIVES

- **Primary:** To evaluate the efficacy of NovoSeven® (rFVIIa) in reducing disability and improving clinical outcome by preventing early hematoma growth in patients with acute ICH.
- **Secondary:** To evaluate the safety of NovoSeven® (rFVIIa) in reducing disability and improving clinical outcome by preventing early hematoma growth in patients with acute ICH.

## STUDY DESIGN

# Drug Data Sheets

## Telavancin (ARBELIC™, TD-6424, AMI-6424)

**Study Title:** A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Telavancin versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to Methicillin-Resistant *Staphylococcus aureus*

**Study Sponsor:** Theravance, Inc.

**Study Personnel:**

<b>Investigator-</b>	Joseph Govert, MD	(ID# 970-6730)
<b>Coordinators-</b>	Linda Brown, RN	(ID# 970-7901)
	Sally Everett, RN	(ID# 970-1006)

**Study Objectives:** *Primary:* To compare the efficacy and safety of telavancin to vancomycin in the treatment of adults with Gram-positive hospital-acquired pneumonia (HAP) with an emphasis on patients with infections due to methicillin-resistant *Staphylococcus aureus* (MRSA).

*Secondary:* To pool the data from this study with those from a second study of identical design (protocol 015) and to assess the superiority of telavancin to vancomycin in patients with MRSA infection.

**Chemistry:** Telavancin is a lipoglycopeptide antibiotic. Each vial of telavancin contains telavancin 250 mg, hydroxypropyl beta cyclodextrin (HP- $\beta$ -CD) 2.5 g (to aid solubility), mannitol 312.5 mg and sodium hydroxide and/or hydrochloric acid (to adjust pH).

**Mechanism of Action:** Telavancin is rapidly bactericidal with multiple mechanisms of actions. First, telavancin, like vancomycin, tightly binds the aglycone core structure to the cell wall intermediate, Lipid II, terminating in the dipeptide D-Alanyl-D-Alanine. This binding event is believed to sequester the enzyme substrate, thus causing inhibition of the formation and subsequent cross-linking of the peptidoglycan layer. The resultant loss of cell wall tensile strength renders the bacteria incapable of compensating for external changes in osmotic pressure, which in turn leads to cell rupture and death. It is over 10-fold more potent on a molar basis than vancomycin in inhibiting peptidoglycan synthesis in intact cells. Additionally, telavancin disrupts bacterial cell membrane function, including dissipation of transmembrane potential and increases in permeability.

**Pharmacokinetics:** Telavancin has a favorable pharmacokinetic profile. The observed half-life was 7 to 9 hours. Plasma concentrations increase in direct proportion to the administered doses with minimal accumulation and departures from linearity. Renal excretion is the major route of elimination. In subjects with severe renal impairment, the plasma clearance of telavancin was about 50% less than healthy subjects.

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**Dosage:** Subjects will be randomized in a 1:1 ratio to telavancin 10 mg/kg once a day IV for 7 – 21 days or vancomycin 1 g every 12 hours IV for 7 – 21 days. Placebo “dummy” infusions of dextrose 5% water (D5W) will be used to maintain the blind. For patients with polymicrobial infections involving Gram-negative and/or anaerobic bacteria in addition to Gram-positive organisms for which the study medication is being used, aztreonam and/or metronidazole therapy, respectively, should be used. Piperacillin-tazobactam or imipenem may be administered for Gram-negative coverage ONLY if aztreonam is not appropriate due to unacceptable levels of resistance.

**Contraindications:** There are no known contraindications.

**Precautions:** Telavancin is formulated with cyclodextrin. Therefore, avoid use of agents containing a cyclodextrin solubilizing agent such as IV itraconazole or voriconazole.

**Adverse Effects:** The most commonly observed adverse events, largely mild in severity and reversible, were taste disturbance (metallic taste), headache and nausea. At higher doses (15 mg/kg), vomiting and infusion-associated reactions characterized as “red-man syndrome” were reported in 15% of subjects, largely females. Telavancin produced a small, but statistically significant prolongation of the QTc interval compared to vehicle control when administered to healthy volunteers.

**Drug Interactions:** Telavancin exhibits weak inhibitory effects on CYP3A and 2D6. There were no significant drug-drug interactions with concomitant administration of either aztreonam or metronidazole.

**Drug/Lab Interactions:** Telavancin interferes with dye and reagent strip methods for urine protein quantification. When telavancin is present in high concentrations in urine, the possibility of false positive results for urine protein exists.

Telavancin interferes with prothrombin time (PT) and activated partial thromboplastin time (aPTT), and when telavancin is present at high concentrations in plasma, the possibility of falsely prolonged results for PT/aPTT exists. For patients that require PT/aPTT monitoring, determinations should be performed near trough concentrations. Alternatively, warfarin can be monitored with a functional Factor X

# MD Order Sheet

Duke University Medical Center - Investigational Drug Service

A Phase II, Multicenter, Double-Blind, Placebo-Controlled, Safety,  
Tolerability and Pharmacokinetic Trial of Study Drug in Moderate Insect-Foot-in-Mouth Disease  
(FeelGood Pharmaceuticals, Inc. Protocol: ABC-001-321)

Alfred E. Neuman, MD

## Medication Order Sheet

**Fax To:** **Investigational Drug Service** **Today's Date:** \_\_\_\_\_  
**Sharon Ellison, RPh, PharmD (ID #3394)** **Voice #: 684-3543**  
**Gregory Westby, RPh (ID # 1210)** **Fax #: 681-2740**  
**Malphus Stroud, CPhT (ID # 7898)**

Subject Name: \_\_\_\_\_ History #: \_\_\_\_\_

Subject Screening Number: \_\_\_\_\_ Weight: \_\_\_\_\_ kg Gender: \_\_\_male \_\_\_female

Date of Birth: \_\_\_\_\_ Date and Time Needed: \_\_\_\_\_

Infusion Number: \_\_\_\_\_

### Please Check One:

\_\_\_\_\_ CLOSED – Cohort One: 0.5 mg/kg ABC-001 or Placebo

\_\_\_\_\_ Cohort Two: 0.15 mg/kg ABC-001 or Placebo

\_\_\_\_\_ Cohort Three: 1 mg/kg ABC-001 or Placebo

### IDS Pharmacy to Prepare/Dispense:

Normal Saline 100 ml

containing

Blinded Study ABC-001 \_\_\_\_\_ mg or Placebo

Administer as directed by protocol with IV administration set provided by sponsor.

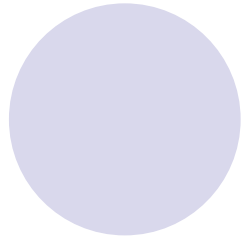
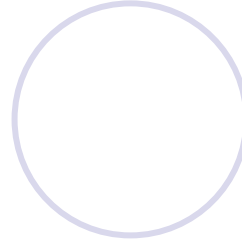
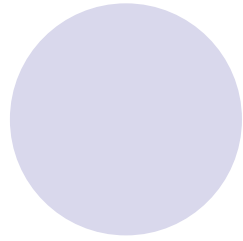
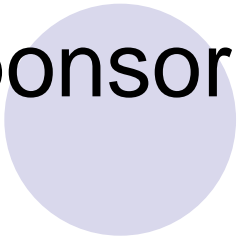
**NOTE -- EXPIRATION: 3 HOURS**

**FOR INVESTIGATIONAL USE ONLY.**

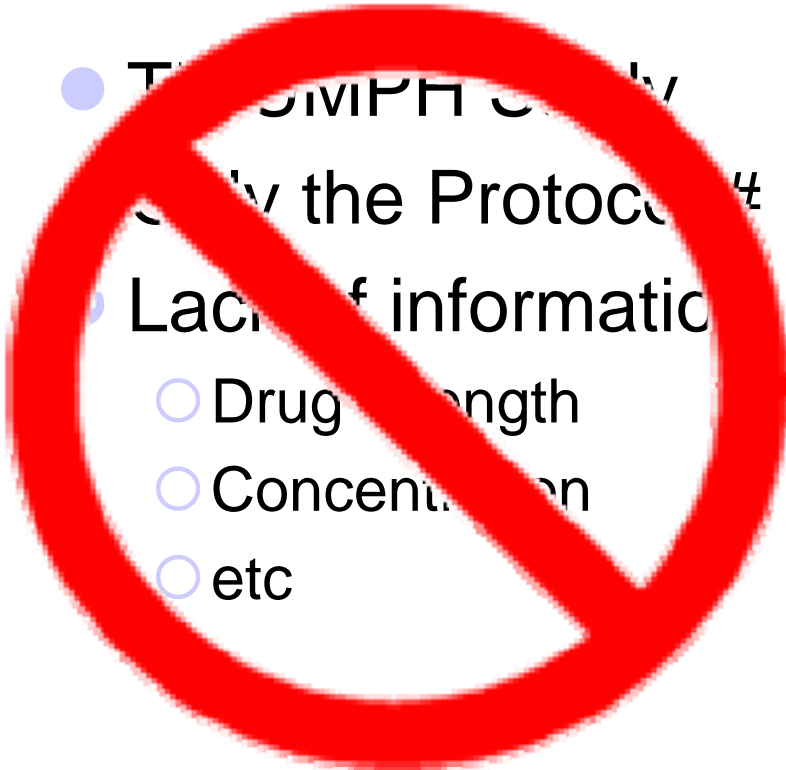
Allow at least one business day for order to be filled. If medication is required in less than one business day, please fax the order and call IDS.

\_\_\_\_\_  
(NOTE: This prescription is only valid when signed by a licensed prescriber) MD

# Sponsor labeling



- The SIMPLIFY study
- Study the Protocol #
- Lack of information
  - Drug strength
  - Concentration
  - etc



# Our Labeling

**IDS 846:** PEDIATRIC HEART NETWORK: Infant Single Ventricle Trial  
Page Anderson, MD (919)684-8111 (ID# 970-2051)

Name: \_\_\_\_\_ ID No: **1502**-\_\_-\_\_-\_\_-\_\_ Room: \_\_\_\_\_

## **Enalapril 1 mg/ml or Placebo Oral Suspension**

Administer 0.2 mg/kg (0.87 mg) orally or via tube every 12 hours.

**Total dose = 0.87 ml** *FOR INVESTIGATIONAL USE ONLY*

Do Not Begin Administration After: September 7, 2005

Prepared by the DUMC Investigational Drug Service 684.3543

# Key Personnel/ 1572 issues

- <http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm>
- Institutions would not be considered "engaged" in human subjects research (and would not need an Assurance) if their involvement is limited to the following:
- Institutions whose employees or agents (i) **perform commercial services for the investigators** (or perform other genuinely non-collaborative services meriting neither professional recognition nor publication privileges), and (ii) **adhere to commonly recognized professional standards for maintaining privacy and confidentiality** (e.g., an appropriately qualified laboratory performs analyses of blood samples for investigators solely on a commercial basis).

# IRB Policy



- IRB members who are listed as a member of the Key Personnel of a study but whose study-related activities are limited to (i) the performance of commercial services for the investigators (or performing other genuinely non-collaborative services meriting neither professional recognition nor publication privileges), while (ii) adhering to commonly recognized professional standards for maintaining privacy and confidentiality (e.g., an appropriately qualified laboratory performs analyses of blood samples for investigators solely on a commercial basis) **would be permitted to participate in the presentation and deliberations associated with the IRB's review of the research protocol.**

Bonnie M. Lee

Associate Director for Human Subject Protection Policy

Good Clinical Practice Program, FDA

- The purpose of being listed on the 1572 is to capture information about individuals who, as part of an investigative team, will be assisting the investigator and who make a **direct and significant contribution to the data**. Hospital staff, including nurses, residents, or fellows and office staff who provide ancillary or intermittent care but who do not make a direct and significant contribution to the data do not need to be listed individually.

# The Budget Process

Brief Study Title \_\_\_\_\_ IDS # \_\_\_\_\_

Contact Person \_\_\_\_\_ Phone \_\_\_\_\_

Date Prepared \_\_\_\_\_ Prepared By \_\_\_\_\_ Reviewed By \_\_\_\_\_

Set Up Fee Quoted: \_\_\_\_\_ Quarterly Maintenance Fee Quoted: \_\_\_\_\_

Dispensing/Preparation Fees: \_\_\_\_\_

Drug & Packaging Fees: \_\_\_\_\_

## Set – Up Fee Budget Elements

	Yes (1 unit)	No (0 units)	Number Applicable
Is drug new to IDS?			
Is study double-blind?			
Is design double-dummy?			
Will patients receive multiple doses?			
How many pharmacy areas will be involved?			
Are any of the drugs controlled substances?			
Will IDS prepare a randomization code?			
Will IDS prepare Patient Teaching materials?			
Other extraordinary requirements?			
<b>Total = number of Yeses + Number applicable</b>			

Assign a set up fee as follows:

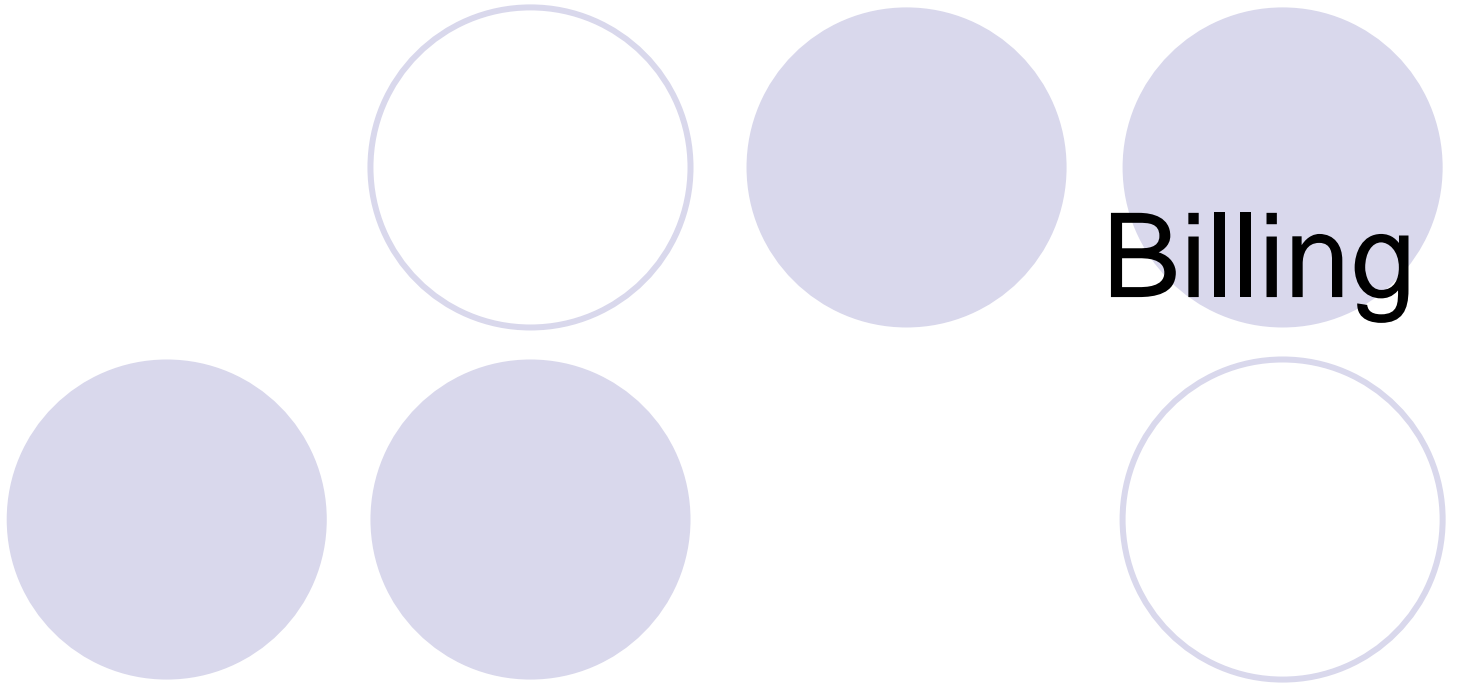
Total Score	Set-Up Fee
1-3	\$300
4-6	\$600
7-9	\$900

## Maintenance Fee Budget Elements

	Yes (1 unit)	No (0 units)	Number Applicable
How many pharmacy areas are involved?			
Is this a multiple dose study?			
Is 24-hour availability for IVRS randomization by IDS personnel required?			
Will used items be returned to IDS?			
Will used items be stored by IDS?			
Is refrigerator or freezer storage required?			
Will monitoring visits be scheduled more frequently than once per quarter?			
For number of patients expected to enroll at Duke, assign a score as follows:	Number of patients	Score	Score Assigned
	1-10	1	
	11-25	2	
	26-50	3	
	51-75	4	
	76-100	5	
	> 100	6	
<b>Total = Number of Yesses + number of pharmacy areas + score from number of patients</b>			

Assign a quarterly maintenance fee as follows:

Total Score	Quarterly Maintenance Fee
1-4	\$ 75
5-8	\$ 150
9-12	\$ 225
> 12	\$ 300 or as negotiated





# Monitoring Appointments

- Directly or through coordinator
- As much in advance as possible
- Not on Mondays
- Nor Friday afternoons

# Frequently Asked Questions/Issues

- Do we need an IND?
- Do we have to use IDS?
- Original forms SOP
- Who is oncall? (Page 970-3394 to find out)
- What materials does IDS need?
- When do you need them?
- How long do you keep records?
- CPOE...
- Duke Compounding Facility (formerly P&P)

# IDS Features and Benefits

- IDS can benefit your study experience by:
  - Reducing overall costs
  - Assuring regulatory compliance
  - Assuring inventory control
  - Reducing unnecessary sponsor demands
  - Eliminating risk due to unsafe medication practices
  - Randomization and non-distribution services
  - Assuring safe forms and label design
  - Help develop education plans for clinical staff providing care, and more...

# How to contact us...

- Room 0101-B, South Hospital, Yellow Zone
- Phone: (919) 684-3543
- Fax: (919) 681-2740
- Pagers
- Emails: [sharon.ellison@duke.edu](mailto:sharon.ellison@duke.edu)  
[gregory.westby@duke.edu](mailto:gregory.westby@duke.edu)

Your Questions?

