NON-INTERVENTIONAL STUDY PROTOCOL
Study Information

Title	Healthcare Professional Survey to Assess the Effectiveness of Additional Risk Minimization Measures for Prescribing and Administration of Concentrated Insulin Human (Humulin® R U-500 vial) using the dedicated U-500 insulin syringe
Version identifier	Version 1
Date of last version	December 13, 2017
Active substance	Insulin Human
Medicinal product(s):	Humulin® R U-500 vial using the dedicated U-500 insulin syringe
Research question and objectives	This study aims to evaluate the impact of the Dear Health Care Provider (DHCP) letter on prescriber understanding about the risk of potential dosing errors associated with the use and administration of Humulin® R U-500 vial using the dedicated U-500 insulin syringe.
Country of study	United States

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1 List of Abbreviations

Abbreviation	Definition
CI	Confidence Interval
DHCP	Dear Health Care Provider
FDA	U.S. Food and Drug Administration
HCP	Healthcare professional
IRB	Institutional Review Board
KAB	Knowledge, Attitudes, and Behaviors
No.	Number
rDNA	Ribosomal Deoxyribonucleic Acid
RMiP	Risk Minimization Plan
SA	Schlesinger Associates
SD	Standard Deviation
SOPs	Standard Operating Procedures
UAT	User Acceptance Testing

2 Responsible Parties

Principal Investigator of the Protocol

Name, degree(s)	Title	Affiliation	Address
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3 Admendments

Amendment or update No.	Date	Section of study protocol	Amendment or update	Reason
N/A				

4 Milestones

Milestone	Planned date
Start of data collection	Estimated January 2018
End of data collection	Estimated February 2018

5 Rationale and Background

Humulin® R U-500 is a concentrated formulation of a polypeptide hormone structurally identical to human insulin. Developed using rDNA technology, the product has been marketed since 1996 in 20 mL vials, indicated to improve glycemic control in adults and children with diabetes mellitus requiring more than 200 units of insulin per day.[1] It has proven to be of particular benefit for patients with insulin resistance because the concentrated formulation allows for delivery of a higher dose in a reasonable volume. As insulin resistance worsens, greater doses are required to meet glycemic goals and patients may face challenges in subcutaneous administration of their medicine.[2]

Although the concentrated formulation has been shown to be safe and effective when used as directed, there have been serious medication errors with Humulin® R U-500 in the past.[1,3,4] Errors have been attributed to dispensing, prescribing, and administration. The majority of instances have resulted from dosing confusion, with the most serious events occurring among patients who experience hypoglycemia from overdosing. Less frequent serious adverse events have been attributed to failures of glycemic control due to underdosing or from drug-drug interactions.

In November 2016, Becton, Dickinson and Company (BD™) launched the U-500 dedicated syringe for patients who use the Humulin® R U-500 insulin vial to reduce the risk of dosing errors. In conjuction, Lilly introduced updated product labeling that supported the use of the U-500 insulin syringe with the Humulin® R U-500 insulin vial. This updated labeling included new information healthcare professionals (HCPs) must be familiar with for informing their patients about safe use. The package insert and other information disseminated to providers draws on experience with the insulin syringe application to date. For example, dosing and administration errors have been reported in patients using U-100 insulin syringes or volumetric, for example, tuberculin, syringes with the Humulin® R U-500 insulin vial.

This study is an initial evaluation of the effectiveness of a risk minimization plan (RMiP) conducted within 18-months of product launch, designed to meet a post-market commitment to the Food and Drug Administration (FDA) for the new insulin syringe product and Humulin® R U-500 vial. The study focuses on Lilly's communication with HCPs, and specifically prescribers (endocrinologists and prescribing primary care physicians, nurse practitioners, and physician's assistants).

Through an online survey, the study will query knowledge of and outcomes related to the Dear Health Care Provider (DHCP) letter (Appendix I) sent to prescribers and pharmacists following the product launch. The DHCP letter summarizes prescriber actions related to the U-500 insulin syringe. The actions include necessary prescription practices and instructions for patients that will ensure safe use of Humulin® R U-500 vial with the dedicated U-500 insulin syringe.

Early evaluation of communications constituting part of risk mitigation measures have evolved toward an emphasis on process measures. This is important because it may be difficult to detect actual impacts on relatively low-frequency medication errors across the first year or longer of an intervention. Surveys, particularly those conducted closely following implementation, focus on the extent to which the program has been executed, the intended impacts on behavior, and assessments of clinical knowledge or comprehension of risks contained in the communication. The FDA has recommended a knowledge, attitudes, and behavior survey (KAB) as a sufficient assessment tool in most cases.[5]

This KAB survey is designed to capture three of four elements appropriate to learning evaluations identified by the FDA: [6]

- *Reaction* – How satisfied are physicians with communications materials, and did they actually receive and utilize them?
- *Learning* – What knowledge about risks have they learned or had reinforced, and how comprehensible are the messages about risks and the need to communicate those risks to patients?
- *Planned Behavior* – What changes (or intention to change) do physicians make in the areas of patient instruction and recognizing the significant potential for dosing errors?

The objectives of the fourth element *Results* (collecting concrete public health outcomes of interest such as reductions in medication dosing errors), exceed the scope of a survey of this type. Additionally, 18 months may be an insufficient period for detecting informative and compelling results on actual risk reduction.

6 Research Question and Objectives

The research questions motivating this study relate to how well the distribution of the DHCP letter has proceeded in the early post-launch period and how well that communication material conveys the most significant risks of Humulin® R U-500 vial using the dedicated U-500 insulin syringe to prescribers. The study also evaluates prescriber understanding about important patient education about those risks. As noted above, this early evaluation focuses on process measures related to reaction, learning, and planned behavior.

The primary study objective is to evaluate the impact of the DHCP letter on prescriber understanding about the risk of potential dosing errors associated with the use and administration of Humulin® R U-500 vial using the dedicated U-500 insulin syringe.

Retention and comprehension by HCPs of the following specific safety messages will be tested in line with this objective. Specifically, HCPs must:

- prescribe the U-500 insulin syringe to patients using the Humulin® R U-500 insulin vial.

Additionally, HCPs should[1]:

- **prescribe the dose in units of insulin and inform patients of their dose in units of insulin;**
- **inform patients that only the U-500 insulin syringe should be used with the Humulin® R U-500 insulin vial and advise patients NOT to switch between types of syringes because it may increase the risk of dosing errors;**
- **educate patients that no dose or volume conversion is needed with U-500 insulin syringe;**
- instruct patients to maintain an adequate supply of U-500 insulin syringes;
- inform patients that in the event of running out of U-500 insulin syringes they should NOT attempt to dose with another type of syringe, but instead call their pharmacist or healthcare professional immediately for further instruction.
- consider prescribing the Humulin® R U-500 KwikPen® to patients who may not be able to understand these precautions or may desire a more certain means of controlling dosing.

The secondary objectives include:

- assessing the proportion of HCPs receiving and reading the DHCP letter and their reactions to the risk mitigation communication content.
- querying prescriber intentions regarding patient education around safe use of the Humulin® R U-500 vial using the dedicated U-500 insulin syringe.

[1] Key safety messages are in bold

7 Research Method

7.1 Study design

This is a cross-sectional survey to be conducted in the United States. Eligible HCPs will have received the DHCP letter in November 2016 and subsequently prescribed the Humulin® R U-500 vial using the U-500 insulin syringe. The HCPs who received the DHCP letter include endocrinology specialists, primary care physicians, advanced practice registered nurses, nurse practitioners, and physician assistants who have prescribed Humulin® U-500 (in vial dosage forms) during the 12 months prior to the U-500 insulin syringe product launch. A random sample of HCPs will be recruited to participate in the survey from the list of HCPs who received a DHCP letter via email. The HCP survey will be administered online.

7.2 Setting

The assessment survey will be executed and the analysis completed within approximately 18 months of the product launch.

Eligible HCPs will receive an email invitation from Schlesinger Associates (SA) to participate (Appendix II). The invitation will include an overview of the rationale for the survey, information on how to access and complete the survey online, privacy information and include a link to the survey. The average survey is expected to take approximately 15 minutes to complete.

The invitation will also indicate that HCPs will be compensated with an incentive card having a $50 value. All those providing screening information are eligible, with the exception of HCPs who are licensed and practice in Minnesota, Vermont, Massachusetts or the District of Columbia and Advanced Practice Registered Nurses (APRNs) in Connecticut in accordance with state laws. HCPs from these states can elect to participate, although they will not be paid. HCP-identifying information will be utilized for the purposes of providing payment and will be managed by Sclesinger Associates (SA).

HCPs eligible for compensation, who complete the screening questions, will be mailed their honorarium. Additionally, HCPs will be emailed a letter thanking them for their time and effort. The email will also include a link to the DHCP letter on the correct use of Humulin® R U-500 vial using the dedicated U-500 insulin syringe and a link to the correct answers to safety message questions (Appendix III).

7.2.1 Population

The initial population in scope for selection consists of the 29,184 HCPs who were sent a DHCP letter for the U-500 insulin syringe and prescribe the U-500 insulin syringe within 12 months of the survey launch date. Schelsinger Associates will implement a panel match strategy to identify HCPs with a valid email address, as initial recruitment will be implemented via email only.

Of those matched, 1,000 HCPs will initially be randomly selected in order to obtain 200 completed surveys with an anticipated response rate of 20%. Reminder invitations will be sent to

those who have not responded to the survey. The response rate will be monitored throughout the data collection period not to exceed 8 weeks. If any of the 1,000 email invitations are not deliverable, then they will be replaced.

If there are fewer than 200 completed surveys two weeks after survey launch, the study team will decide on what additional follow-up measures will be implemented. Such measures may include a second random selection of HCPs from the eligible matched list. Alternatively, phone or direct mail may be employed to augment low response and ensure a full sample. If the response rate is higher than 20% then no additional follow-up or HCP sampling will be required.

HCPs who complete the screener and qualify for the survey are included in the survey's analysis population. Data collected on the screener and on the survey will be available for this analysis population.

HCPs who complete the screener, but do not qualify to participate in the survey are included in the screen failures analysis. These HCPs may fail the screener because they indicate that they have not met one of the inclusion/exclusion criteria. Data collected on the screener will be available for this population.

7.2.2 Inclusion Criteria

HCPs must meet the following criteria to be eligible for inclusion in the survey:

- HCPs who received the DHCP letter.
- HCPs who prescribed the Humulin® R U-500 vial using the dedicated U-500 insulin syringe.
- HCPs must be able to read and respond to the survey in English.

7.2.3 Exclusion Criteria

HCPs meeting any of the following criteria will not be included in the survey:

- HCPs or their immediate family members are current or past employees of Lilly, Covance, SA, or the FDA.
- HCPs have participated in the Humulin® R U-500 vial using the dedicated U-500 insulin syringe survey before.
- HCPs who have qualified and completed the Humulin® R U-500 KwikPen® Survey (launched in July 2017)

7.2.4 Survey Period

An 8 week data collection is estimated to recruit the HCPs and obtain approximately 200 completed surveys.

7.3 Variables

As specified in the project objectives above, the survey captures HCPs' knowledge of the safety messages in the risk minimization communication letter as primary outcomes. While these questions contain an option for "I don't know," response will be dichotomized for analysis as correct or incorrect across seven statements. An additional multiple-choice item provides two correct options with an incorrect choice outlining an unsafe practice for dealing with insulin syringe malfunction. HCPs will also be asked about the source of their knowledge of product risks, using a single multiple choice question.

Additionally, the survey instrument has questions about the HCP's reaction to the communication. HCPs will be asked if they recall receiving the DHCP letter. Additional reactions are queried in a series of four questions with Likert response scales for those confident about having read the material. As there are no correct answers for these appraisals of the DHCP letter, responses will be analyzed descriptively.

Finally, the HCP survey includes three questions about patient counseling and planned behavior. The series includes two multiple choice questions and a dichotomous query about the the prescriber's intent to counsel patients.

The survey also captures demographic characteristics that include age, gender, geographical location, HCP specialty, and practice information. Personal contact information about an HCP will only be collected by SA where applicable for mailing payment to study participants; this information will not be included in study datasets.

7.4 Data Sources

Responses to the HCP Survey comprised of closed-ended questions or statements with multiple response choices (i.e., questions or statements asking the HCPs to choose from a defined list of responses) and HCP information contained in the sampling frame are the source of the study data.

Screening questions:

- Prescribed the Humulin® R U-500 vial using the dedicated U-500 insulin syringe
- Aware of having received DHCP letter
- HCPs or their immediate family members are not current or past employees of Lilly, Covance, SA, or the FDA
- Didn't previously participate in the survey
- Qualified and completed the Humulin® R U-500 KwikPen® Survey
- Agree to participate

Data on demographic characteristics:

- Age group
- Gender
- Role at facility
- Facility type
- State or territory of practice
- HCP medical specialty (e.g., General Internal Medicine, Endocrinology/Diabetology, Family Medicine, and Other)
- Number of years practicing medicine/nursing (e.g., <5 years, 5-10 years, 11-15 years, and >15 years)
- Number of patients prescribed the Humulin® R U-500 vial using the dedicated U-500 insulin syringe (e.g., 0, 1-5, 6-10, 11-20, and >20)

Data pertaining to evaluation of the effectiveness of the risk minimization measures:

The survey includes questions/statements that will assess HCP understanding about the risks and associated behavior of the HCPs to minimize these risks. The understanding level and behaviors will be analyzed using descriptive statistics and confidence intervals (CIs) and will be used to determine the effectiveness of the risk minimization measures:

- Awareness of the DHCP letter on the correct use of Humulin® R U-500 vial using the dedicated U-500 insulin syringe
- Understanding of the safety messages
- Self-reported practices and intentions with respect to communication of the safety messages in clinical practice

The RMiP will be considered effective if the majority of HCPs demonstrate they are aware of the key safety messages communicated for the Humulin® R U-500 vial using the dedicated U-500 insulin syringe.

7.5 Study Size

A sample size of 200 HCPs will provide a confidence interval of ±5.49 percentage points at the 95% confidence level if 80% of the HCPs answered the key risk questions correctly, as shown in Table 1.

The confidence interval for the percent correct response is calculated using the finite population correction factor as: $p \pm 1.96[\sqrt{(p(1-p))}/\sqrt{n}]*\sqrt{(N-n)/(N-1)}$ where p is the proportion of HCPs answering the survey question correctly, N is the population size, and n is sample size.

Table 1: Table of Confidence Intervals by Sample Size and % Answering the Question Correctly

-95% Confidence Level-

	Percent Answering the Question Correctly				
Sample Size	**50%**	**60%**	**70%**	**80%**	**90%**
50	±13.83	±13.55	±12.67	±11.06	±8.30
100	±9.75	±9.55	±8.94	±7.80	±5.85
150	±7.94	±7.78	±7.28	±6.35	±4.77
200	±6.86	±6.72	±6.29	±**5.49**	±4.12
250	±6.12	±6.00	±5.61	±4.90	±3.67

Note: These calculations were performed assuming a population size of 10,000. The confidence intervals are not greatly altered with varying population size assumptions.

Additional measures will assess review and understanding of the RMiP, but these measures do not drive the sample size calculation.

7.6 Data Management

All data collected during the survey will be held confidentially by SA. They will program and host the survey. The survey data will be transferred from SA to Covance via a secure method and stored on the secure SAS server within the study area. Covance's data transfer standard operating procedures (SOPs) will be followed. Only study staff who need the data to complete the analysis will be granted access. All statistical programs will be developed using SAS® Version 9 (or later) software. No identifiable information will be required from any HCP, but will be collected if they are eligible and wish to receive payment.

The survey is programmed to ensure the HCP must respond to all relevant questions. Skip logic as well as the ability to mark only one response or multiple responses are part of the programming for the survey administration and minimize the occurrence of data entry errors. There will be no queries to HCPs for this project. Datasets and analytic programs will be kept on the secure Covance SAS server.

7.7 Data Analysis

Evaluation of the effectiveness of the DHCP letter in conveying key safety information for Humulin® R U-500 vial using the dedicated U-500 insulin syringe will be primarily descriptive in nature. Frequency distributions with 95% CIs will be calculated for responses to all questions that address the survey objectives. Responses to each question relating to the key safety messages will be categorized as "Correct response" and "Incorrect response". Additionally, "I don't know" is categorized as an incorrect response unless otherwise specified.

7.7.1 Analysis Data Sets

The Analysis Set will consist of all eligible HCPs who complete the screener and qualify for the survey. Data collected on the screener and on the survey will be available for this analysis population. The Analysis Set will be used to assess all the study objectives unless otherwise stated.

The Screening Set will consist of all HCPs who complete the screener, but do not qualify to participate in the survey. Data collected on the screener (i.e., demographic information) will be available and presented for the Screening Set.

The following sections will be reported as part of the analysis.

7.7.2 Survey Administration Statistics

Survey administration statistics will be reported. This summary will include the number of:

- Survey invitations issued by and specialty
- Survey invitations returned due to incorrect email address
- HCPs who responded to the invitation to participate in the survey
- Ineligible HCPs along with the reasons for ineligibility
- HCPs eligible for participation in the survey
- Eligible HCPs who completed the survey

These values will be summarized with the counts and percentage of HCPs. The percentage will be based on the number of HCPs in previous categories which will be detailed in the table shells. For example, the percentage of ineligible and eligible HCPs will be based on the number of HCPs responding to the survey.

7.7.3 Demographic and Other Baseline Characteristics

Demographic variables will be summarized for all HCPs, the Analysis Set and the Screening Set. These will include the distribution of HCPs by:

- Age groups
- Gender
- Practice setting
- State/region
- Medical specialty
- Years in medical practice
- Number of patients prescribed the Humulin® R U-500 vial using the dedicated U-500 insulin syringe.

These categorical variables will be summarized with frequencies and percentages.

7.7.4 Primary Objectives and Endpoints

Frequencies and percentages, along with 95% CIs will be used to assess HCP retention and comprehension of the risks associated with Humulin® R U-500 vial using the dedicated U-500 insulin syringe. The denominator will be the number of HCPs who complete the survey. Specifically, primary endpoints are the proportion of those correctly answering each of the following statements[1]. Response options are either True/False or multiple choice.

- **It is appropriate to prescribe U-500 insulin syringe to patients using the Humulin® R U-500 insulin vial.**
- **When prescribing Humulin® R U-500 vial using the dedicated U-500 insulin syringe it is important to inform patients of their dose in units of insulin because it allows patients to draw up to that same unit marking on the U-500 insulin syringe.**
- **When using the Humulin® R U-500 vial using the dedicated U-500 insulin syringe, patients do not need to convert the dose.**
- **It is important to instruct patients that they should only use the U-500 insulin syringe with the Humulin® R U-500 insulin vial.**
- **Patients should not switch between types of syringes because it may increase the risk of dosing errors.**
- Patients need to know their dose in units of insulin.
- It is important to instruct patients to maintain an adequate supply of U-500 insulin syringes.
- In the event of running out of the dedicated U-500 insulin syringes, patients should not attempt to dose with another type of syringe, but instead call their pharmacist or healthcare professional immediately for further instruction.

The RMiP will be considered effective if the majority of HCPs demonstrate they are aware of the key safety messages communicated for Humulin® R U-500 vial using the dedicated U-500 insulin syringe by correctly answering these statements.

7.7.5 Secondary Objectives and Endpoints

The secondary endpoints will also be assessed descriptively with frequencies and percentages. Confidence intervals for proportions will not be calculated where appraisals cannot be dichotomized to a correct or incorrect answer.

All HCPs, whether or not they have read, or recall having read the DHCP letter, will be asked a multiple choice question about the source of information (e.g. professional knowledge) or approach (e.g. guessing) that best characterized their response to the safety questions.

Reactions to the DHCP letter based on the degree of agreement or disagreement with statements about the information will be responded to only by those HCPs affirming that they have read the DHCP letter. Specifically, statements to be evaluated include:

- The discussion of prescribing information encouraged me to better counsel my patients about the use of U-500 insulin syringe.
- I found the description of product features to be useful.
- I learned better how to respond to possible adverse events as a result of reading this communication.
- I found the summary of important safety information to be a useful extension of product labeling.

Planned behavior will be addressed by two questions. The first queries the HCP's understanding about the need for patient counselling with U-500 insulin syringe while the second directly asks the HCP about their intention to counsel patients.

7.8 Quality Control

User Acceptance Testing (UAT) will be performed on the survey using a sample of approximately 8-10 HCPs. The UAT procedure is designed to assess comprehension among HCPs regarding the words and phrases used in select survey questions and response options. UAT will also assess the clarity of the survey questions as presented to HCPs and the interest and acceptance of the surveys among all prospective HCPs and flow and ease of completing the surveys.

Online administration allows for additional randomization of response options, offsetting potential order effects. Questions pertaining to reading and reactions to the DHCP letter are asked after the risk questions. During the course of online administration, the back-button on the survey is disabled preventing alteration of responses once reviewed and entered.

The data are also checked as part of the UAT process to make sure that all of the data collected within the online survey environment are correctly extracted from the system for use in the programming environment.

In addition to the UAT processes for the survey instrument and programming environment, several other strategies will be used to ensure data quality. The randomized sampling strategy outlined above helps ensure representativeness, minimize volunteer bias, and provides an additional means for ensuring valid data. In the analysis, demographic criteria are summarized for those who met survey inclusion criteria against those who did not meet the criteria.

All statistical programs will be developed and validated using good programming practice guidelines. This is a one-time cross-sectional survey with HCPs, there is no risk to any patients, and Institutional Review Board (IRB) approval is not required.

Covance will follow Covance's standard operating procedures in the creation and quality control of all tables, listings, figures and analyses. Lilly or its designee will review all tables, listings, and figures for accuracy.

7.9 Limitations of the Research Methods

The sample may remain subject to an undetermined selection bias because volunteers are drawn from a market panel match of the full population known to have received the DHCP letter. However, the HCPs will be randomly selected from Schlesinger Associates' market-panel matches, which may mitigate this concern somewhat.

Additionally, performance on the survey may or may not be reliant on the HCP's recall of whether or not the DHCP letter was received. It is possible that they have acceptable understanding of the risks and appropriate behaviors despite not having read the DHCP letter. Lilly will explore these possibilities with variables described in Section 7.3.

As with most survey data, information is self-reported and therefore susceptible to reporting biases. There may ultimately be discrepancies between what HCPs report about their intentions and what they ultimately do.

Lastly, this survey is administered only online. While the majority of the HCPs within the sampling frame are likely to have an email address, not everyone on the list has an email address listed, likely precluding their participation.

7.10 Measures to Minimize Bias

HCPs completing the screener and meeting the U-500 insulin syringe survey eligibility requirements will be directed to participate in the online survey. Survey biases will be minimized through carefully constructed, non-leading survey questions, and a thorough internal validation process.

Online forms will be programmed such that HCPs have access to only one survey question at a time; once a question is submitted, HCPs do not have the option of revisiting it, i.e., the back button is disabled. Lists of response options will be randomized to minimize the potential for positional bias. HCPs who do not complete the survey will have their access to the survey terminated, and the observation is left incomplete.

Correct responses will be provided to the physicians following completion of their survey, allowing for feedback on performance and reinforcing correct information and/or best clinical practice.

8 Protection of Human Subjects

8.1 Personal Information and Consent

All data collected during the survey will be held confidential by SA and used only for the purposes stated in the survey instructions. HCP names and addresses are only collected for the purposes of payment, if applicable, after the survey is completed. By answering the first question of the survey ("Do you agree to take part in this survey about the Humulin® R U-500 vial using the dedicated U-500 insulin syringe?") after reading the introductory message, HCPs are acknowledging informed consent for participation in the research study.

8.2 HCP Withdrawal

HCPs can decline to participate or stop taking the survey at any time. Only completed surveys that include all questions answered will be included in the analysis. HCPs will be informed that their answers to the survey questions will not affect their ability to prescribe Humulin® R U-500 vial using the dedicated U-500 insulin syringe.

8.3 Central Institutional Review Board (IRB)

This protocol is exempt from IRB requirements.

9 Management and Reporting of Adverse Events/Adverse Reactions

This study does not involve data collection on clinical endpoints for patients of the individual HCPs. The online survey does not include any questions that could potentially identify a safety event, nor does it provide a free text field where study HCPs could specify information that may constitute a safety event (defined as an adverse event, product complaint, or other reports; e.g. overdose, abuse, misuse, off label use, pregnancy exposures, breast feeding exposures, lack of drug effect, medication error and suspected transmission of infectious disease). Free text fields available following completion of the survey will be used by SA only to collect contact information to provide payment of honoraria.

10 Plans for Disseminating and Communicating Study Results

A final report for describing the survey objectives, detailed methods, results, discussion, and conclusions will be developed at the end of the survey.

11 References

1. Eli Lilly & Company. Information for the Physician, Humulin R Regular U-500 (Concentrated) Insulin Human Injection, USP (rDNA Origin) Description. Available at http://pi.lilly.com/us/humulin-r-u500-pi.pdf.

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5. FDA. 2013. Background Materials for REMS Standardization and Evaluation Public Meeting: REMS Evaluation. Available at http://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm361888.htm.

6. Framework cited above and adapted from Kirkpatrick DL, et al. 1959. Techniques for evaluating training programs. *Journal of American Society of Training Directors* 13 (3):21–26. The best known public health outcomes evaluation approach is outlined in Glasgow R, et al. 1999. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *American Journal of Public Health*. 89(9):1322-27, although this is not suited for an early stage evaluation of a health care professional communication plan.

Appendix I Dear Healthcare Provider Letter on the correct use of U-500 insulin syringe

Humulin® R U-500
insulin human injection
500 units/mL

October 2016

IMPORTANT PRESCRIBING INFORMATION

Subject: A U-500 dedicated syringe is now available for your patients who use the Humulin® R U-500 insulin vial to reduce the risk of dosing errors.

Dear Healthcare Professional:

Eli Lilly and Company (Lilly) is writing to inform you of important safety information about prescribing and administration of Humulin R U-500 insulin (U-500). Dosing and administration errors have been reported in patients using U-100 insulin syringes or volumetric, for example, tuberculin, syringes with the U-500 vial.

To reduce the potential for these errors, a Becton, Dickinson and Company (BD™) U-500 insulin syringe is now available for your patients who use the vial presentation of U-500. **This new U-500 syringe MUST BE prescribed as it will not be available Over The Counter (OTC). No dose or volume conversion is needed when using this syringe, so it is vital that patients know the UNITS OF INSULIN prescribed. You should prescribe in units of insulin, which will allow patients to draw their dose to that same unit marking on the U-500 insulin syringe.** Alternatively, the Humulin® R U-500 KwikPen® is approved and available for use.

Prescriber Actions

- Prescribe the U-500 insulin syringe to your patients using the U-500 vial, or consider switching them to the Humulin R U-500 KwikPen.
- Prescribe the dose in units of insulin and specify that the U-500 insulin syringe should be used. Prescribing in units of insulin allows patients to draw up to that same unit marking on the U-500 insulin syringe.
  - For example, if your patient currently doses 150 units of U-500 using a U-100 syringe, they are drawing to the 30 mark on the syringe to deliver 150 units of insulin. If the patient doses with a volumetric syringe, they are currently drawing to 0.3 mL for 150 units of insulin. With the new U-500 insulin syringe, they should draw to the 150 mark on the syringe for 150 units of insulin.
- Inform your patients that they should use ONLY this U-500 insulin syringe with the U-500 vial. Advise your patients NOT to switch between types of syringes because it may increase the risk of dosing errors.
- Since this U-500 insulin syringe is available by prescription only, instruct your patients to maintain an adequate supply of U-500 insulin syringes. In the event of running out of U-500 insulin syringes, they should NOT attempt to dose with another type of syringe, but instead call their pharmacist or healthcare professional immediately for further instruction.

Please see Important Safety Information on last page and accompanying Full Prescribing Information.
Please see Instructions for Use included with the vial.

Lilly

Humulin® R U-500
insulin human injection
500 units/mL

Features of dedicated U-500 syringe

- The dedicated syringe packaging contains language to use only the U-500 insulin syringe with the U-500 vial.
- Syringes are individually packaged in a green blister pack, rather than polybags.
- The dedicated syringe has a green cap. (U-100 insulin syringe cap is orange.)
- There is a U-500 concentration mark on syringe collar for easy identification. Note: the U-500 vial also includes a green concentration mark, and green vial collar and flip-cap.
- The syringe is designed to dose up to 250 units (0.5 mL) of U-500. Numeric unit markings by 25-unit increments up to 250 are provided with each small mark corresponding to 5-unit increments.

Reporting Adverse Events and Product Complaints

Healthcare professionals and patients are encouraged to report adverse events in patients taking Humulin R U-500 insulin to The Lilly Answers Center at 1-800-545-5979. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

This letter is not intended as a complete description of the benefits and risks related to the use of Humulin R U-500 insulin. Please refer to the enclosed Full Prescribing Information.

Please contact Lilly at 1-800-545-5979 if you have any questions about the information in this letter or the safe and effective use of Humulin R U-500 insulin vial or U-500 insulin syringe.

Sincerely,

Robert Baker, MD
Vice President, Global Patient Safety

Please see Important Safety Information on last page and accompanying Full Prescribing Information.
Please see Instructions for Use included with the vial.

Lilly

Humulin® R U-500
insulin human injection
500 units/mL

Important Safety Information for Humulin R U-500

Contraindications

- Humulin R U-500 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to Humulin R U-500 or any of its excipients.

Warnings and Precautions

- **Dosing Errors:** Extreme caution must be observed in measuring the dose of Humulin R U-500 because inadvertent overdose may result in serious adverse reaction or life-threatening hypoglycemia.
- **Hyperglycemia, Hypoglycemia, or Death Due to Dosing Errors in the Vial Presentation:** Medication errors associated with the Humulin R U-500 vial resulting in patients experiencing hyperglycemia, hypoglycemia, or death have been reported.

  Dispensing
  - Instruct patients to always inspect insulin vials to confirm that the correct insulin is dispensed including the correct brand and concentration.
  - For the Humulin R U-500 vial, particular attention should be paid to the 20-mL vial size, prominent "U-500" and warning statements on the vial label, and distinctive coloring on the vial and carton.

  Prescribing
  - Dosing errors have occurred when Humulin R U-500 was administered with syringes other than a U-500 insulin syringe. Patients should be prescribed U-500 syringes for use with Humulin R U-500 vials. The dose of Humulin R U-500 should always be expressed in units of insulin.

  Administration
  - Instruct patients to always check the insulin label before each injection.
  - Use only a U-500 insulin syringe with Humulin R U-500 to avoid administration errors. Do not use any other type of syringe to administer Humulin R U-500. Adhere to administration instructions.
  - Instruct the patient to inform hospital or emergency department staff of the dose of Humulin R U-500 prescribed.
- If using the Humulin R U-500 KwikPen, patients should be counseled to dial and dose the prescribed number of units of insulin (NO dose conversion is required).
- DO NOT transfer Humulin R U-500 from the Humulin R U-500 KwikPen into any syringe for administration. Overdose and severe hypoglycemia can occur.
- **Never Share a KwikPen or U-500 Syringe Between Patients,** even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.
- **Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen:** Changes in insulin, manufacturer, type, or method of administration should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased.
- **Hypoglycemia:** Hypoglycemia is the most common adverse reaction associated with insulin, including Humulin R U-500. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Severe hypoglycemia may develop as long as 18 to 24 hours after an injection of Humulin R U-500. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important, such as driving or operating other machinery.
  - Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual.
  - Early warning symptoms of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system, or in patients who experience recurrent hypoglycemia.
  - The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation. As with all insulin preparations, the glucose lowering effect time course of Humulin R U-500 may vary in different individuals or at different times in the same individual and depends on many conditions.
  - Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.
- **Hypersensitivity and Allergic Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Humulin R U-500. If hypersensitivity reactions occur, discontinue Humulin R U-500; treat per standard of care and monitor until symptoms and signs resolve.
- **Hypokalemia:** Insulin use can lead to hypokalemia that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may

Warnings and Precautions, continued

be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

- **Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists:** Thiazolidinediones (TZDs), which are PPAR-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Observe patients for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

Adverse Reactions

- Adverse reactions include hypoglycemia, allergic reactions, lipodystrophy, injection site reactions, weight gain, peripheral edema, and immunogenicity.

Drug Interactions

- Some medications may alter glucose metabolism and may necessitate insulin dose adjustment. Signs of hypoglycemia may be reduced or absent in patients taking antiadrenergic drugs. Particularly close monitoring may be required.

Use in Specific Populations

- **Pregnancy Category B:** While there are no adequate and well-controlled studies in pregnant women, evidence from published literature suggests that good glycemic control in patients with diabetes during pregnancy provides significant maternal and fetal benefits.
- **Pediatric Use:** There are no well-controlled studies of use of Humulin R U-500 in children. Standard precautions as applied to use of Humulin R U-500 in adults are appropriate for use in children.
- **Geriatric Use:** There are no well-controlled studies of use of Humulin R U-500 in geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia.
- **Renal or Hepatic Impairment:** Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

Dosage and Administration

- Prescribe Humulin R U-500 ONLY to patients who require more than 200 units of insulin per day.
- Humulin R U-500 is available as a KwikPen or a multiple dose vial. Patients using the vial must be prescribed the U-500 insulin syringe to avoid medication errors.
- DO NOT perform dose conversion when using the Humulin R U-500 KwikPen. The dose window of the KwikPen shows the number of units of Humulin R U-500 to be injected and NO dose conversion is required.
- DO NOT perform dose conversion when using a U-500 insulin syringe. The markings on the syringe show the number of units of Humulin R U-500 to be injected. Each marking represents 5 units of insulin.
- Instruct patients using the vial to use only a U-500 insulin syringe and on how to correctly draw the prescribed dose into the syringe. Confirm that the patient has understood these instructions and can correctly draw the prescribed dose with their syringe.
- Advise the patient to read the Patient Information and Instructions for Use.
- Instruct patients to always check the insulin label before administration to confirm the correct insulin product is being used.
- Inspect Humulin R U-500 visually and only use if the solution appears clear and colorless.
- Administer Humulin R U-500 subcutaneously two or three times daily approximately 30 minutes before a meal. Rotate injection sites to reduce the risk of lipodystrophy.
- Individualize the dose of Humulin R U-500 based on metabolic needs, blood glucose monitoring results, and glycemic control goal.
- Do NOT administer Humulin R U-500 intravenously or intramuscularly.
- Do NOT mix Humulin R U-500 with other insulins.

Storage

- Protect from heat and light. Do not freeze. Do not use Humulin R U-500 after the expiration date stamped on the label.
- Humulin R U-500 Vials: Unopened vials of Humulin R U-500 should be kept in a refrigerator. Opened (in-use) vials of Humulin R U-500 should be kept in the refrigerator or at room temperature and used within 40 days of opening. Throw away any opened vial after 40 days of use, even if there is insulin left in the vial.
- Humulin R U-500 KwikPen: Unopened Humulin R U-500 KwikPens should be kept in a refrigerator. Opened (in-use) Humulin R U-500 KwikPens should be kept at room temperature and used within 28 days of opening. Do not refrigerate opened KwikPens. Throw away any opened KwikPen after 28 days of use, even if there is insulin left in the pen.

See accompanying Full Prescribing Information.
See Instructions for Use included with the vial.

HMU500 HCP ISI 27SEP2016

Appendix II Invitation to Participate and Healthcare Professional Survey

Email Welcome

[PROGRAMMING NOTE:]

On behalf of Eli Lilly and Company (Lilly), we would like to invite you to participate in a voluntary research survey about concentrated insulin human (Humulin® R U-500 vial) using the dedicated U-500 insulin syringe. The survey is part of a post-marketing commitment between Lilly and the Food and Drug Administration (FDA) to assess the effectiveness of the risk minimization tool.

This survey should take approximately 15 minutes to complete. Once you begin the survey you will need to answer all questions. If you are ready to begin the survey at this time, please click the survey link below. If not, please return to this site when it is convenient for you.

If you are eligible and complete the survey, you will be compensated in the amount of $50 for your time and participation. You are under no obligation to complete this survey. Your answers to the questions in this survey will not affect your ability to prescribe Humulin® R U-500 vial using the dedicted U-500 insulin syringe.

Compensation for participation is not permitted in Vermont, the District of Columbia, Massachusetts, or Minnesota in accordance with state or federal law. Please be aware that healthcare professionals (HCPs) who are licensed and practice in these states or territories as well as Advanced Practice Registered Nurses (APRNs) in Connecticut will not be eligible for compensation for survey participation.

Your privacy will be protected. However, research survey records may be inspected by the FDA or other regulatory agencies. To the extent permitted by applicable laws and regulations, the records identifying you will not be made publicly available. All the information you provide will be kept strictly confidential. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither Lilly nor its contractors will sell, transfer, or rent your information.

If you are interested in participating and to find out if you are eligible, please click on the following link below:

[SURVEY LINK]

Note: Do not use the browser's back button during this survey. You cannot change your responses once the answer is submitted.

HCP Screener

1) Do you agree to take part in this survey about the Humulin® R U-500 vial using the dedicated U-500 insulin syringe?

1 ❒ Yes

2 ❒ No

[PROGRAMMING NOTE: If participant answers "2", then terminate]

a) Did you qualify and complete the Humulin® R U-500 KwikPen® survey previously launched in July 2017?

1 ❒ Yes

2 ❒ No

3 ❒ I don't know

[PROGRAMMING NOTE: If participant answers "1" or "3", then terminate]

2) Have you ever participated in **THIS** survey (first available January 2018) for the Humulin® R U-500 vial using the dedicated U-500 insulin syringe before?

1 ❒ Yes

2 ❒ No

3 ❒ I don't know

[PROGRAMMING NOTE: If participant answers "1" or "3", then terminate]

3) Are you or were you employed, or are your immediate family members employed by Eli Lilly and Company, Schlesinger Associates, Covance Market Access, or the United States Food and Drug Administration?

1 ❒ Yes

2 ❒ No

3 ❒ I don't know

[PROGRAMMING NOTE: If participant answers "1" or "3", then terminate.]

4) Which state or territory are you licensed to practice in?

[PROGRAMMING NOTE: Provide a drop down list of States and territories]

[PROGRAMMING NOTE: Include logic to insert region in the back-end for all locations based on selection]

5) What is your role in the management of patients with diabetes?

1 ❒ Physician
2 ❒ Advanced Practice Registered Nurse
3 ❒ Nurse Practitioner
4 ❒ Physician Assistant
5 ❒ Other

6) Please choose an option about your participation in this survey.

1 ❒ I will participate in the survey and would like to be paid.
2 ❒ I will participate in the survey but will not to be paid.

[PROGRAMMING NOTE: Compensation for participation is not permitted for HCPs in Vermont, District of Columbia, Massachusetts, or Minnesota, as well as, for Advanced Practice Registered Nurses (APRNs) in Connecticut. HCPs should be advised that they are ineligible for payment based on these restrictions, if appropriate.]

7) Are you involved in the management of patients with diabetes? This includes prescribing medications to treat diabetes or providing education to help manage diabetes.

1 ❒ Yes
2 ❒ No

[PROGRAMMING NOTE: If participant answers "2", then go to Q8 and terminate after Q14.]

8) What is your primary medical specialty?

1 ❒ General Internal Medicine
2 ❒ Endocrinology/Diabetology
3 ❒ Family Medicine

4 ❒ Other

9) How many years have you been in practice as a physician, physician assistant, or nurse practitioner since completing your medical/nursing education?

1 ❒ Less than 5 years
2 ❒ 5 – 10 years
3 ❒ 11 – 15 years
4 ❒ More than 15 years

10) In what type of facility do you work?

1 ❒ General Practice
2 ❒ Hospital
3 ❒ Other

11) Approximately, how many patients have you prescribed the U-500 insulin syringe?

1 ❒ 0
2 ❒ 1 – 5
3 ❒ 6 – 10
4 ❒ 11 – 20
5 ❒ More than 20

[PROGRAMMING NOTE: If participant answers "0", then terminate after Q14.]

12) Which of the following age groups best describes you?

1 ❒ Less than 30
2 ❒ 30 – 39
3 ❒ 40 – 49
4 ❒ 50 – 59
5 ❒ 60 – 69
6 ❒ 70 or older

13) What is your gender?

1 ❒ Male
2 ❒ Female

14) Are you aware that you received a Dear Health Care Provider letter from Eli Lilly and Company about the Humulin® R U-500 vial using the dedicated U-500 insulin syringe?

1 ❒ Yes
2 ❒ No
3 ❒ I don't know

[PROGRAMMING NOTE: End of screening questions]

[PROGRAMMING NOTE: Begin survey questions]

Survey

The following questions are about U-500 insulin syringe.

15) Please answer True, False, or I don't know for each of the following statements regarding the Humulin® R U-500 vial using the dedicated U-500 insulin syringe.

		True	False	I don't know
a	Prescribers must prescribe a U-500 insulin syringe to patients using the Humulin® R U-500 insulin vial.	○ 1	○ 2	○ 3
b	When prescribing the Humulin® R U-500 vial using the dedicated U-500 insulin syringe it is important to inform patients of their dose in units of insulin because it allows patients to draw up to that same unit marking on the U-500 insulin syringe.	○ 1	○ 2	○ 3
c	Patients need to know their dose in units of insulin.	○ 1	○ 2	○ 3
d	When using the Humulin® R U-500 vial using the dedicated U-500 insulin syringe, patients may need to convert the dose when prescribed as labeled.	○ 1	○ 2	○ 3
e	It is important to instruct patients that they should only use the U-500 insulin syringe with the Humulin® R U-500 insulin vial.	○ 1	○ 2	○ 3
f	Patients should not switch between types of syringes because it may increase the risk of dosing errors.	○ 1	○ 2	○ 3
g	It is important to instruct patients to maintain an adequate supply of U-500 insulin syringes.	○ 1	○ 2	○ 3

[PROGRAMMING NOTE: Randomize the list above a-g.]

16) In the event that a patient runs out of the dedicated U-500 insulin syringes, what would you instruct the patient to do? (please select all that apply)

1 ❒ Use another type of syringe to withdraw the insulin from the Humulin® R U-500 insulin vial
2 ❒ Contact a pharmacist or healthcare professional immediately for further instruction
3 ❒ Contact the Lilly Answer Center for more information at 1-800-545-5979

17) My answers to the preceding questions about the Humulin® R U-500 vial using the dedicated U-500 insulin syringe were based on…(**choose ALL that apply**)

1 ❒ Professional knowledge about the use of human insulin products
2 ❒ Previous experience with insulin syringe technology in other Lilly products such as Humalog
3 ❒ Familiarity with the Humulin® R U-500 vial using the dedicated U-500 insulin syringe package inserts
4 ❒ Knowledge gained from interaction with Lilly's sale representative
5 ❒ Knowledge gained from the Humulin Dear Health Care Provider letter.
6 ❒ Guessing
7 ❒ Online information

[PROGRAMMING NOTE: Randomize the response options above 1-7.]

18) Did you read the Dear Health Care Provider letter provided to you by Eli Lilly and Company on "Important Prescribing Information" for the Humulin® R U-500 vial using the dedicated U-500 insulin syringe (insulin human)?

1 ❒ Yes
2 ❒ No
3 ❒ I don't recall

[PROGRAMMING NOTE: If participant answers "1" then go to following items based on agreement scales. If participant answers "2" or "3" skip the following series of 4 items identified under 19 and go to question 20.]

19) Based on your reading of the Dear Health Care Provider letter provided to you by Lilly, please evaluate your reaction to the material you received by indicating the level of your agreement or disagreement with the following statements:

a. The discussion of prescribing information encouraged me to better counsel my patients about the use of the Humulin® R U-500 vial using with the dedicated U-500 insulin syringe.
   1 ❒ Strongly disagree
   2 ❒ Disagree
   3 ❒ Neutral
   4 ❒ Agree
   5 ❒ Strongly Agree

b. I found the description of product features to be useful.
   1 ❒ Strongly disagree
   2 ❒ Disagree
   3 ❒ Neutral
   4 ❒ Agree
   5 ❒ Strongly Agree

c. I learned better how to respond to possible dosing errors as a result of reading this communication.
   1 ❒ Strongly disagree
   2 ❒ Disagree
   3 ❒ Neutral
   4 ❒ Agree
   5 ❒ Strongly Agree

d. I found the summary of important safety information to be a useful extension of product labeling.
   1 ❒ Strongly disagree
   2 ❒ Disagree
   3 ❒ Neutral
   4 ❒ Agree
   5 ❒ Strongly Agree

20) Do you or another healthcare professional at your practice discuss the safe use of the Humulin® R U-500 vial using the dedicated U-500 insulin syringe with patients receiving their initial prescription?

1 ❒ Yes, I directly counsel my patients.
2 ❒ Patient counseling about the use of medicines or new products is the responsibility of a nurse or diabetes educator in my practice setting.
3 ❒ No, counseling is generally not provided for patients about the use of prescription insulin.

21) Given what you know about the Humulin® R U-500 vial using the dedicated U-500 insulin syringe, mark the best answer:

1 ❒ The product's ease of use and advanced safety features make counseling by prescribers unnecessary.
2 ❒ Prescribers should counsel their patients about the safe use of this product.
3 ❒ Any potential medication error is likely to result from dispensing and counseling is best left to pharmacists in their interactions with patients.
4 ❒ U-500 insulin syringe is not fundamentally different from any other syringe and patients with experience in self-administration can use the product safely based on product instructions.

22) Based on my knowledge about the Humulin® R U-500 vial using the dedicated U-500 insulin syringe, I intend to counsel patients on its use.

1 ❒ Yes
2 ❒ No

[PROGRAMMING NOTE: End of Survey Questions]

Closing

[PROGRAMMING NOTE: Display the following when complete or screen failed]

[PROGRAMMING NOTE: Ask respondent for their contact information so payment can be mailed]

Thank you for providing your participation. Your survey is considered complete.

Appendix III Thank - You Letter and Correct Survey Responses

Dear [FIRST NAME] [LAST NAME]:

On behalf of Eli Lilly and Company, the maker of concentrated insulin human (Humulin® R U-500 vial), we want to thank you for taking part in the insulin human (Humulin® R U-500 vial) using the dedicated U-500 insulin syringe survey.

Additionally, to ensure that survey participants have accurate information about the risks of U-500 insulin syringe, we have provided links to the following two documents:

- A copy of the correct answers to the survey questions about the U-500 insulin syringe safety messages
- A copy of the U-500 insulin syringe Dear Health Care Provider (DHCP) letter.

<The correct answers to the survey questions link>

<DHCP letter link>

Sincerely,
The Humulin® R U-500 vial using the dedicated U-500 insulin syringe Survey Team

Correct Survey Responses to U-500 insulin syringe

Please answer True, False, or I don't know for each of the following statements regarding the Humulin® R U-500 vial using the dedicated U-500 insulin syringe.

		True	False	I don't know
a	Prescribers must prescribe a U-500 insulin syringe to patients using the Humulin® R U-500 insulin vial.	■	○	○
b	When prescribing the Humulin® R U-500 vial using the dedicated U-500 insulin syringe it is important to inform patients of their dose in units of insulin because it allows patients to draw up to that same unit marking on the U-500 insulin syringe.	■	○	○
c	Patients need to know their dose in units of insulin.	■	○	○
d	When using the Humulin® R U-500 vial using the dedicated U-500 insulin syringe, patients may need to convert the dose when prescribed as labeled.	○	■	○
e	It is important to instruct patients that they should only use the U-500 insulin syringe with the Humulin® R U-500 insulin vial.	■	○	○
f	Patients should not switch between types of syringes because it may increase the risk of dosing errors.	■	○	○
g	It is important to instruct patients to maintain an adequate supply of U-500 insulin syringes.	■	○	○

In the event that a patient runs outs of the dedicated U-500 insulin syringe, what would you instruct the patient to do? (please select all that apply)

- ❒ Use another type of syringe to withdraw the insulin from the Humulin® R U-500 insulin vial
- ■ Contact a pharmacist or healthcare professional immediately for further instruction
- ■ Contact The Lilly Answer Center for more information at 1-800-545-5979